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SOME OF THE MEDICAL CENTERS OF SOUTH AMERICA

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Foreword

In the Jan. 13, 1940 issue of *The Lancet* (London, England) Prof. Grey Turner published a most interesting account of his visit to some of the medical centers in South America. The article describes the excellent work being done by South American Surgeons, and for this reason as well as because it would prove of great value to North American surgeons contemplating a visit to South American clinics, the chairman of the Editorial Board asked Professor Turner to prepare a similar article on the same subject for publication in the ARCHIVES. Professor Turner graciously complied, and his contribution, part of it taken from *The Lancet*, follows.

These brief notes are the record of a visit, made in company with my wife, to Buenos Aires, Argentina, and other South American republics and cities during September 1939 under the aegis of the British Council for the Promotion of Cultural Relationships. The voyage from England, with calls in Portugal, Madeira and Brazil, was in every way delightful, though the last few days were darkened, in more senses than one, by the threat of war.

When we arrived at Montevideo, the principal city of Uruguay, after sailing for several days under wartime conditions, it was delightful to be greeted by H. B. M. Minister Mr. Millington-Drake and by the surgeons of the city, who had most thoughfully arranged a deputation to welcome us. A further surprise was in store, for we were soon joined by Dr. Oscar Ivanissevich and Dr. Castro O'Connor, who throughout proved such an admirable and efficient secretary and who came on behalf of the faculty of medicine of the University of Buenos Aires to offer us a further welcome and to chaperone us during the concluding stages of our journey up the river Plate. When we landed at our destination, Prof. José Arce (fig. 1) and several others were waiting with a further warm welcome, and from that moment until we left, nearly two weeks later, we met with the greatest kindness, and a handsome motor car was always at our disposal.

My mission was to deliver a series of lectures, to make contacts in professional and academic circles and to see as much as time would

permit of the work of the hospitals and ancillary institutions. Incidentally, these activities were interspersed with numerous social functions, lavish hospitality being shown on every side.

Buenos Aires ranks high in the scale of great cities, not only because of its size but because of its fine layout and notable architectural features. It was a surprise to find such a city with between two and three million inhabitants, for, though it is over 6,000 miles from the shores

Fig. 1.—Prof. José Arce, director of the Institute of Clinical Surgery of Buenos Aires.

of Great Britain, it is a sort of mixture of London, Paris and New York. There are wide open spaces, many public gardens and no end of fine statues. Much land along the river bank is being reclaimed and laid out as public parks with broad boulevards and flower borders, and every scrap of spare ground seems to be looked after, even though at some not very distant date it may be destined to be built on. The whole town breathes a fine civic spirit, which indeed seemed to be general in most of the South American republics which we visited. The numerous hospitals are for the most part old buildings in the Spanish

style, with patios, colonnades and ample open spaces, laid out with flower beds and shrubs between the pavilions. But in most cases new blocks are springing up in the grounds of the original institutions, and, quite apart from new buildings, alterations have been made to bring the various departments up to date. Fortunately, as yet nothing has been done to overshadow the original style, which reminds one so much of the old days of Spanish domination. Inside these old hospitals, what struck one more than anything else was the way that every hole and corner had been put to some useful purpose. It was remarkable to find parts of the corridors, window recesses and odd corners converted to some useful purpose, apparently without regard to a build-

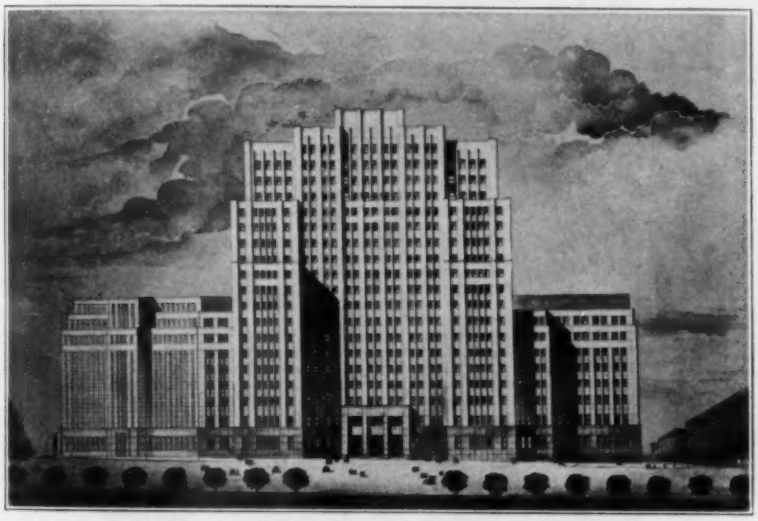

Fig. 2.—Model of the new Institute of Clinical Surgery in the course of erection in Buenos Aires.

ing scheme but simply that the new-found space might serve the end in view without delay. The use of light tiles and light paint converts dark corners into bright spaces, and of course the plentitude of marble and of sunshine is a great help. But the days of some of the old hospitals seem to be numbered, and just opposite the Institute of Clinical Surgery a large modern building which is springing up will form a hospital center and medical school on the American plan (figs. 2 and 4). The central part is to be eighteen stories high, and, as the illustrations show, the other parts are in keeping. Many of the clinics as they are today remind one of the Continental style and are more of the French than of the Nordic pattern, and the caps and aprons worn by the professors and their staff are very reminiscent of Parisian days. In the well appointed clinic of Prof. José Arce the influence of that

master of organization and fount of inspiration was obvious on every hand. There seemed to be no shortage of competent assistants, and it would appear that the idea of sticking to the parent hospital attaches a great many of the senior men to the various posts and probably means that there are always lots of well trained men willing and anxious to continue at hospital work in the hope of attaining preferment. But the atmosphere was good, and the clinic seemed to claim the attach-

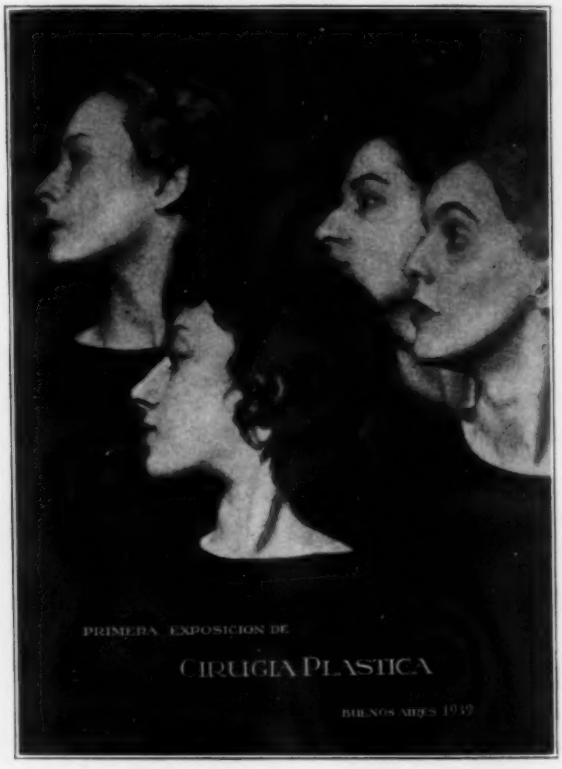

Fig. 3.—Cover of the catalog of the exhibition of plastic surgery.

ment of everybody about it. A good deal of the teaching is done in rather an old-fashioned amphitheatre, which is also used for operations, but the tutorial work is conducted in smaller classes in the wards. At operations one notices the frequent use of local and spinal anesthesia, but it was explained that this was largely due to the disinclination of the Argentino to lose consciousness; it is a wide awake country, and the patients like to know what is going on! But general anesthesia is gaining a foothold; one saw some of the latest machines in occasional use, and at least one member of the medical profession is devoting

himself entirely to work as a specialist in anesthetics. The operating lists are singularly like those at home except that, of course, the surgical management of hydatid diseases still takes a prominent place, though we were told that the disease is not nearly so frequent as in the immediate past. Surgery of the lung is coming into its own, and it was interesting to find that neurosurgery is mostly in the safe hands of a Harvey Cushing pupil and disciple. In the clinic of Arce, plastic surgery has been largely developed by Dr. Oscar Ivanissevich, and just at the time of my visit an exhibition of photographs, diagrams and models (fig. 3) dealing with plastic surgery and its results was being held in an empty ward, which in ordinary times would accommodate some 25 or 30 patients. Nearly all the photographs were in color and were illuminated from behind, and they made a very fine show. The municipal art gallery had loaned some oil paintings of appropriate nudity, and these helped to enliven the more technical exhibits. The exhibition was arranged to commemorate the twenty-fifth anniversary of Professor Arce's occupation of the chair of surgery in the university and to express the warm feelings of his pupils for the stimulating example of their maestro. The inauguration ceremony was attended by representatives from other towns in the Argentine and from the neighboring republic of Uruguay. On that occasion I was glad to be given the opportunity of saying something about the general principles involved in this branch of surgery.

The medical clinic of Professor Mariano Castex is a very active unit, and there were numbers of enthusiastic assistants, all most anxious to exhibit their work. As in other departments, I was struck with the way small spaces and odd corners had been used to accommodate laboratories, examination rooms, secretarial offices, etc. One small ward was devoted entirely to diseases of the peripheral vascular system, and there I saw numbers of elderly men with advanced vascular starvation, in some cases with impending loss of the toes or part of a foot as the result of gangrene. Professor Castex explained that they made a special study of these conditions and that by various means, but especially by use of subcutaneous injections of carbon dioxide, they were getting very good results; in fact, during the previous two years it had not been necessary to do a single formal amputation of a limb, although some patients had lost a small part of the foot. In nearly every case recovery was complete enough to allow the patient to resume his previous occupation. There was ample evidence of activity in other branches of medical work, such as the treatment of carcinoma of the bronchus and lung (which they find to be very common), bronchiectasis and nephritis and the geographic distribution of renal calculi, etc. Each clinic seems to have its own roentgen department, and the results shown me were very good indeed.

At the Rawson Hospital, with its new department of surgery, I saw Prof. Enrique Finochietto, who is doing some very nice work. Before operating the professor demonstrated the steps by a series of excellent colored drawings which he had himself prepared. These were exhibited on an easel in the theater; being turned over one by one, they provided a most effective guide to the work proposed. Finochietto's technic for gastrectomy by the Billroth no. 1 method is well known and largely used in South America, and it was a treat to see it completed by such a master. The local anesthesia was perfect. I noticed that Duval's lung forceps was largely used and was certainly a most effective handle for the viscera. Some remarkable and curious esophageal conditions had been collected for my inspection. Many of the patients come from the campo, that is, the region of enormous open plains which forms so much of the country of the Argentine. The agricultural workers there do not seem to bother much about their physical complaints until they are most obvious, which probably accounts for the extremely advanced state of many of the pathologic conditions which Professor Finochietto's assistants were able to demonstrate. At the Hospital Ramos Mejia I met Dr. A. Ceballos, a recent visitor to Great Britain and an enthusiastic worker. The theater there is of the ultramodern type; any but the most intimate visitors are entirely excluded from the floor and find places in a gallery which is really outside the room and from which they look down on the operations through plate glass screens, communication being established through the medium of loudspeakers. Though probably not contemplated, it was not surprising to look up and see visitors whiling away the tedium of looking at some complicated proceeding from this considerable distance while enjoying a cigaret. Dr. Ceballos demonstrated the case of a young boy on whom he had recently carried out a total pneumonectomy, with an excellent result. A visit to the wards showed a new type of construction, with which I was entirely unfamiliar. Inside the long ward there were built partitions extending about 6 feet (1.8 meters) high and surrounding a space large enough to accommodate two beds, which as a rule faced the window. In a long ward this arrangement provides a certain amount of privacy, but it occurred to me that it is probably rather trying for the patients, especially when the sky and the sun are both bright. In the same hospital on another day I met Dr. Robertson Lavalle, whose work on the treatment of tuberculosis of bone has been the subject of discussion for some years. I feel that I cannot usefully comment on his methods, but I was shown 1 or 2 patients with evidence of well developed Pott's disease who had been treated by his technic of bone puncture and who were apparently completely cured, though no fixation by plaster or apparatus of any sort had been employed and no long period spent in bed. Dr.

Lavalle operated on a typical Pott's spine. A bone fragment about 2 inches (5 cm.) long and about ¼ inch (0.6 cm.) thick was cut from the front of the tibia; one side of the spine near the disease was then exposed by an incision about 3½ inches (8.8 cm.) long, as in the first stage of laminectomy. A hole was then made with an instrument like a bradawl from the root of the lamina obliquely forward into the vertebral body just above the main lesion. Into this hole the spigot of tibial bone was driven, and the incision was closed. As soon as the wound had healed the patient was to be allowed to get about freely, without retentive apparatus of any sort. I also saw illustrations and roentgenograms of cured lesions which left one bewildered and wondering. This subject was constantly discussed in the Argentine, and Dr. Lavalle and his disciples seemed to be satisfied about the efficiency of the plan. I could not help feeling that there must be something in this method, and yet what that something is or what is the dividing line between success and failure I am unable to surmise.

At the Hospital Rivadavia, with Dr. A. J. Bengolea, I saw some excellent results in cases of intractable vesicovaginal fistulas following labor, treated by transplantation of the ureters. I also saw many specimens of large gallstones which had passed spontaneously without operation as a result of administration of magnesium sulfate through a duodenal tube. Dr. Bengolea is investigating problems of biliary surgery, for his activities in the field of gynecology and the realm of general surgery seem to be interchangeable. With a British colony of over 50,000, it is not surprising that the British hospital in Buenos Aires is the largest outside the British Isles, and it was nice to find that half of the new hospital with its fine wards and spacious balconies was already completed. The staff, who are all of British origin, are keen and enthusiastic. The buildings of the medical school are delightfully spacious, reminding one of those of the Medical Faculty in the University of Saragossa in Spain. My visit was made in the evening, and in the absence of sun the buildings appeared gloomy. It was very difficult to realize that the enormous lecture theater, after the style of those one sees depicted on the title pages of some of the old folio works on anatomy, was only about a hundred years old. The carved scroll on a canopy above the lecturer's platform was a fine piece of work, which did not seem to be appreciated, though the comfortable seats covered with plush must have been somewhat of an attraction. The days of this particular theater are numbered, for it is to be replaced by a modern theater or series of theaters in the new building which is rapidly rising from the ground in the vicinity (fig. 4). It was easy to lecture to the enthusiastic audience which collected, but one soon realized that punctuality had not become a reflex among professional circles in the Argentine. I spoke in English, using lantern slides and films, and was assured that the great majority of those present under-

stood me quite well, as English is commonly spoken and is at least understood by those in academic circles in Buenos Aires. For the lecturer who must perforce employ English in a foreign country the secret is to talk slowly and distinctly, remembering that it sometimes makes for clarity to take time to give an alternative rendering of some word or phrase. An odd word or two of Spanish or French here and there may dispel an obscurity in a surprising way. In the provincial towns and in Chile the gist of what I said was translated as I went along, but good slides and films with some captions in Spanish went a long way to make up for linguistic deficiencies. The audiences were most attentive and did not appear to mind rather long sessions.

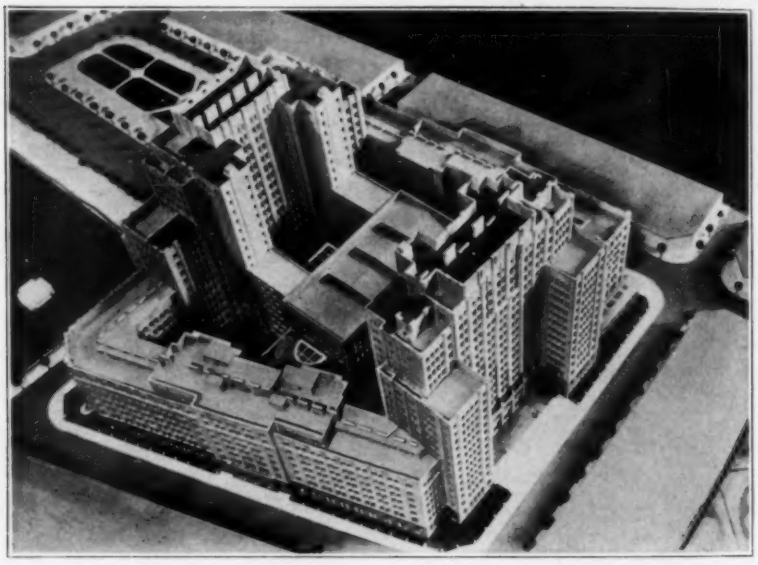

Fig. 4.—Model of the Institute of Clinical Surgery, seen from above.

It was interesting to learn that the medical course in the Argentine is practically free and that the students have some word in the choice of their professors. The exercise of this privilege accounted for a rather noisy meeting which the students were holding in one of the corridors just outside a lecture theater and for an exhortation chalked in big letters on a wall in the school, urging the claims of one teacher rather than another!

The morgue is not usually a very attractive feature of any city, but that certainly does not apply to Buenos Aires, for I do not hesitate to say that it was one of the most interesting places in connection with medicine which it has ever been my privilege to visit. The director has a highly developed artistic sense and a stimulating personality, and

this accounts for the way the building is embellished with marble, stained glass windows and decorated iron work and is further adorned with pictures and statues. There are growing plants, flowers, trickling water and soft lights, and it only requires the enchantment of music and incense to make one think of some scene from the Arabian Nights. The office of the director was much more like the bureau in some great art collection than the administrative office of a dead house. The whole idea is to soften the poignancy of death without destroying its mystery. The institute reflects great credit on everybody concerned, for all the necessary work has been done on the premises. The modeler who makes the death masks was responsible for the statues; another of the staff painted the pictures; the engineer who looked after the refrigerator plant made the decorated iron work, and so on. The postmortem room itself was beautifully clean and was so effectively air conditioned as to be entirely free from smell.

One of the best features is a museum of medical jurisprudence which would have delighted our British medical jurists. The director apologized for its small size, but it is about as large as the war collection at our College of Surgeons Museum in London and appears ample. There is housed a wonderful series of actual specimens illustrating all kinds of wounds and other injuries, burns of all degrees up to complete charring of the body, lightning injuries, the effects of poisoning by chemicals and gases and the conditions causing sudden death. All kinds of crimes were depicted "in the flesh," and some were so realistic as to be revolting. The specimens are beautifully preserved and exhibited, and where necessary there are also wax models, diagrams and photographs. Each exhibit has a full descriptive label, and copies of the complete notes on every specimen are kept in the museum and are readily available. The morgue is, of course, intended for the most part for the reception of bodies sent by the police, but I understand that by request any postmortem examination can be conducted there. The dossier of every subject is complete, and in one folder are all the particulars furnished by the police and the relatives. When available there are copies of the clinical notes, complete lists of the possessions found on the body, careful records of the examination made, records of chemical tests, photographs of the body, newspaper cuttings, letters and, in fact, everything relevant, preserved and kept together. All is most complete and is carefully dated and always readily available. It was an unexpected experience, after an hour or two spent in the building, to be invited to the director's office and to have the opportunity of talking over pathologic experiences seated in comfortable chairs in artistic surroundings and regaled with delicious coffee and cigarets.

A visit to the Institute of Experimental Medicine, which is directed by Prof. Angel Roffo (fig. 5), proved most interesting. This is on the outskirts of the city, where it occupies a very large area (fig. 6). The many pavilions are situated in grounds which are artistically laid out. The name does not quite give the proper impression of the activities of the work carried on here, for large numbers of patients are seen and treated, and the institute deals with problems which arise on the clinical side as well as with experimental and laboratory work. The hospital part contains not only the large outpatient department but wards for

Fig. 5.—Prof. Angelo Roffo with his visitors (September 1939). From left to right, the photograph shows Professor Roffo, Mrs. Grey Turner, Professor Turner and Dr. Castro O'Connor.

resident patients, laboratories, operating theaters and ample provision for treatment by irradiation and all the ancillary methods which may be necessary in cases of malignant disease. The equipment for high voltage roentgen therapy appeared to be complete and adequate, and at the time of my visit they were engaged in installing some newer and very high voltage machines. The professor was hopeful that he had overcome the difficulty about wastage of the tubes as a result of the development of a method of cooling by oil. It was instructive to talk over the results which had so far been obtained. No extravagant claims were made, but

one could judge from the records that the work was done extremely carefully and systematically and that probably the best results obtainable were being secured. To enhance the value of the records extensive use is made of pictorial methods, and in all cases photographs are made not only at the commencement of treatment but repeatedly throughout its course. We heard of remarkable results in some few individual cases, but these one almost comes to expect in cancer clinics, and it is difficult to avoid the conclusion that many of them are in the nature of freak results which are unlikely to be repeated even by employment of exactly the same methods in comparable cases. So far they have had little success in the treatment of malignant disease of the esophagus or of intra-abdominal disease, and the professor appeared to be quite hopeless about the outlook for malignant melanoma. For cancer of the rectum operation is largely employed, but irradiation is used as an adjunct, and

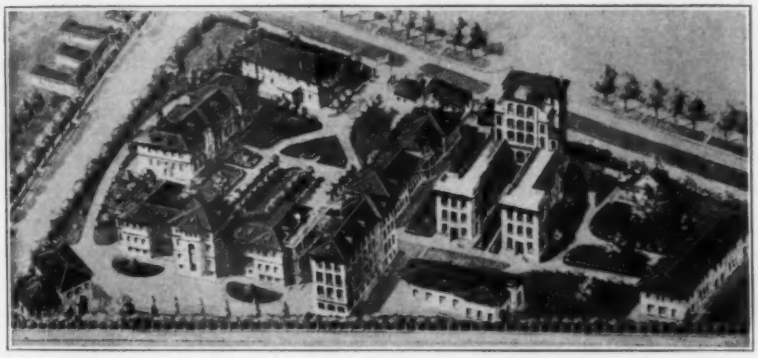

Fig. 6.—Institute of Experimental Medicine in Buenos Aires.

so it is with cancer of the breast and cancer in other situations. I got the impression that close study of the methods would prove of great interest and value. As in all other countries that enjoy a maximum of sunshine, cancers of the skin are very common, and here they can claim a large proportion of excellent results by irradiation, with a minimum of deformity. The professor has been very interested in the problems connected with this particular type of disease, and by examination of the skin by a special lamp he is able to detect those cases in which heavy deposits of cholesterol suggest a tendency to development of malignancy. All the work is checked, and the colored figures of the cutaneous lesions were very convincing. In the institute there is a pathologic museum devoted to malignant disease in all its varieties. In the laboratories they are at the moment particularly interested in the part that tobacco may play as a carcinogenic agent. Quantities of tobacco of all varieties were being investigated, and in every case they had extracted a thick, black,

oily-looking substance which contained the carcinogenic agent in varying proportions; we saw many experimental animals in which various types of surface cancer had been produced by painting with the product.

After this demonstration one could appreciate the idea behind propaganda posters which showed what was supposed to be the carcinogenic agent falling from a cigaret and depicted as flowing like a great black cloud over the greater part of the cancer-ridden globe. A similar substance can be extracted from soot particles from the air. It was quite alarming to see the large quantity of soot which had been collected in one of the filters, though one would have thought that the institute was situated in a particularly soot-free part of a not very sooty city. They have a remarkable collection of tissue cultures which had been going on for a long time, and the study of various problems by this method seems to play an important part in their work.

The record and literary department appears to be complete, for they endeavor to cover the world literature dealing with cancer. The huge pile of reprints from the daily post bag looked most formidable, and we saw a couple of clerks at work going through the articles and making epitomes, which were filed in a card index system, but I wondered if this system were sufficiently personal to be as useful as the labor involved would lead one to expect.

A few hours is far too short a time to spend in this institute, and the interested visitor ought to have two or three days at his disposal to get the most value out of such a visit.

I must just mention the house of the Argentine Medical Society, which occupies something of the same position in the medical community as does the Royal Society of Medicine in London. In addition, it is affiliated with the societies of outlying towns, and it also extends hospitality to other medical societies, which hold their meetings in its fine premises. They have nice lecture rooms, reading rooms, committee rooms and a very good library and are anxious to establish closer connection with the similar institutions in our own country. Dr. Carlos Mainini is the president, and I was told that the flourishing condition of the institute was entirely due to his enthusiasm, his capacity for organization and the tact and industry which he has applied to its development.

No account of Buenos Aires, however brief, should omit some mention of the truly marvelous collection of prehistoric animals preserved in the museum at La Plata, which is just thirty-five miles from the capital.

From Buenos Aires we went down to Montevideo, which is the capital of the Republic of Uruguay. This attractive city is 123 miles by river boat from Buenos Aires, the journey being made over night. The

city has a population of about three quarters of a million, and appears to be a very "go-ahead" place. The medical faculty, which is large and active, is housed in fine buildings after the old spacious Spanish style, with a huge portico and massive marble staircase. The theater where I lectured was large and ornate but had good acoustic properties. I was much struck with the dissecting room, which was a veritable hive of industry, for there are large numbers of students of both sexes, and subjects are plentiful. I must say that I never saw more beautiful dissections in any "rooms" that I have ever visited. There is also a good and quite large anatomic museum. Testut is the usual textbook, but the clinicians complain that the students are expected to spend far too much time in anatomic study and that the subject is presented in too much detail. In nearly all the medical schools that I visited in South America the only whole time professors were the physiologists, so that it was surprising to hear that it was the extent of the anatomic teaching that appeared to be the more criticized. The large hospital is a very old building, also in the Spanish style, but it and the other hospitals are to be replaced by a modern medical center which is now in process of erection and where the buildings tower so high as to be a landmark from all over the city. Nearby is the new municipal Hospital for Infectious Diseases, with a fine range of laboratories for the public health work of the community. Prof. Dr. Horacio Garcia Lagos is head of the surgical department of the principal hospital, and in his service I saw many remarkable examples of hydatid disease, which is still one of the commonest of all the conditions with which they have to deal. It was interesting to see 2 patients operated on by the method of marsupialization, and, though I was struck by the powerful suction pump which was used for evacuating the parasites, I could not help feeling that such a machine might be dangerous in the hands of any but those who are very familiar with its proper use. They use a 2 per cent concentration of the standard (40 per cent) solution of formaldehyde very freely, not only to inject into the cyst before incision but to soak the gauzes which are packed about. Of course all branches of surgical work are represented, and I saw much of interest in genitourinary and bone work. As in Buenos Aires, the relations of the assistants with their chief seemed very cordial, and under his stimulating aegis much good work is being accomplished. The professor has large clinical classes, and the students did not seem to mind that most of the time allotted to his lecture was spent in addressing me in English. It was refreshing to meet Professor Navarro, who, at 76 years of age, is still doing full work in his surgical service and holding the attention of his classes. They have a special night emergency service for the hospitals, and after 8:30 p. m. all cases of acute disease are dealt with in one institution, special surgeons being appointed for

this purpose. The British Hospital is quite an old institution with a fine reputation. The management wisely includes on the staff one of the most respected of the university professors, Dr. Horacio Garcia Lagos, which brings to the institution an academic status often lacking in the smaller hospitals.

Montevideo owes a great deal to the wise guidance, enthusiasm and generosity of H. B. M. Minister Mr. E. Millington-Drake. In his efforts for the welfare of the people he is ably supported by his wife, Lady Effie, and the new maternity wing, which is her gift to the British Hospital, is complete and well designed and will be a great acquisition to the city. Incidentally, let me say that in South America the advantage of maternity departments in connection with hospitals is being widely appreciated.

Throughout the republics football appears to have taken the place of bull fighting, and one was astonished to see a new stadium which is said to be capable of seating 90,000 people, and which is furnished with its own first aid post and hospital.

The activities of the cultural societies is marked both in Buenos Aires and in Montevideo. In both cities I lectured to large audiences, mostly composed of the inhabitants, who study English with avidity in the classes arranged by the society.

The next visit was to Rosario, a large port on the Parana river three and a half hours by rail from Buenos Aires. The city claims half a million inhabitants who are largely occupied in the grain and cattle trades. The principal hospital is old and dull, but the surgical side is very active, and I shall never forget the beautiful gastrectomy which I saw carried out with local anesthesia by Prof. Dr. Oscar Cames. The professor makes a great feature of getting his patients up very early after operations, and I saw a man walking about, dressed in his ordinary clothes, two days after an extensive gastrectomy, which had also been carried out with local anesthesia. When operating for renal calculus they always take a roentgenogram of the exposed kidney. The plate, of a very "quick" variety, is enveloped in sterile wrappings and is actually held against the kidney during the very short exposure which is all that is necessary. The plate is developed at once; they say that it requires only an extra four minutes and that the method often proves very helpful. Many of the patients come from the campo, and diseases and injuries are apt to be far advanced before they reach the hospital. The medical school is large and active, and there one found Professor Lewis with a complete department of physiology. In the town there is a private hospital which is a veritable Mayo Clinic in miniature, and in the library there it was interesting and stimulating to find that English medical books were very popular.

Córdoba, the next stopping place, is not quite such a large town, and is situated 432 miles from Buenos Aires. It is an old city, and the University is proud of the fact that it was the first in the republic and can look back on three hundred years of useful history. Originally a Jesuit college, it possesses a fine old library and a wonderful senate house, where the stalls for the professors are made of beautifully carved solid mahogany. The principal hospital is of the same old Spanish type with which one had become familiar, but it is to be gradually replaced by new pavilions. One of these pavilions is already finished and houses three departments of hospital activity, each on its own floor. We saw the throat and ear department, which is in charge of Dr. Heriberto Wilson. There everything was of the latest, and I was particularly struck by the rooms for the staff, including a departmental library, a lounge, and study rooms, all in addition to the ample suite provided for the professor himself.

Prof. P. L. Mirizzi is of course very well known in connection with his work on cholangiography carried out at the time of operation, and one was shown a wonderful collection of lantern slides illustrating the use of the method in all kinds of cases. Though it was Saturday afternoon, I found the department of physiology at work and was told that in the Argentine the day is not recognized as an academic holiday. I have never seen a department better equipped, in spite of the fact that it was housed in the oldest type of building imaginable, but the plans for a new building are now drawn up, and when complete the Physiological Institute ought to be very fine indeed. Although most of the instruments were from Germany, probably about a third were of English design and manufacture, and it was encouraging to notice a large proportion of English journals and books in the departmental library. Generally speaking, the Argentines are largely pro-British and are much attracted by our methods and our culture.

It was from Cordoba that we made the journey by plane over the Andes. This meant that part of the flight was at a height of between 15,000 and 20,000 feet, but, except for a slightly unpleasant sensation in the ears, it was just as comfortable as sitting in a very well sprung and luxurious motor car. But the grandeur of the Cordillera cannot be appreciated on a journey accomplished so easily, and as a corrective it is necessary to read Darwin's description of his crossing on muleback as related in the "Voyage of the Beagle." On arrival at Santiago we were courteously met by Dr. Fernando Opazo, who came to welcome us on behalf of the university. It was unfortunate that our visit happened to coincide with a great public holiday, which interfered seriously with the work of the hospitals. Nevertheless, we made a considerable tour of many institutions and were struck by the spacious

grounds in which they were situated. The hospital for accidents ("traumatology") is in a new building and is arranged after the style of the similar hospital presided over by Bohler in Vienna. The patients are accommodated in a number of small wards. Skeletal traction is largely employed, and compound fractures are treated without any dressings and certainly seem to do very well. Some very badly injured patients come from the campo and illustrate the difficulties of transport in a country with few railways and poor roads. In the Children's Hospital one saw a great deal of interest; acute osteitis and bone tubercle appeared to be very prevelant. The arrangements of the "Assistance Publique" impressed me very much. There are three principal centers, and all are arranged on much the same plan. The idea is that any sort of emergency case can be taken to these centers, where there is always a competent medical staff on duty. These physicians are all on the staffs of other hospitals and take two and one-half hour periods of duty in rotation throughout the twenty-four hours. Both medical and surgical emergencies are recognized, and the organization is served by an excellent ambulance service. Like "Maxim's," they never close, but the most striking feature is the fact that from about 8 p. m. until 8 a. m. the ordinary hospitals do not take emergencies, which during that period must perforce go to the "Assistance Publique," so that the ordinary hospital services and their patients are not disturbed during the hours of repose. Here they are dealt with, and at the earliest opportunity (it may be within a few hours or it may be after a few days) they are transferred to complete their recovery to the hospital in the district to which they belong. On admission to the station of the "Assistance" they first go through the cleansing department, where road dirt etc. is removed and the patient is washed and provided with hospital garments, and here the preliminary records are made. The operating theaters are always "set" for an operation, so that all that need be done is to remove the towels covering the sterilized instruments, lotion bowls etc., which are laid out in readiness. The records appeared to be most complete, special care being taken with the after-progress. All requisitions are carefully checked so that waste and extravagance can be eliminated. If the system works as well as it has been devised, then it must be good indeed. At a hastily convened meeting of the Society of Hospital Surgeons there was an enthusiastic audience eager to hear something of the progress of British surgery.

The journey home, up the west coast of South America, provided an opportunity for short visits to many places of much interest in several republics. I was particularly struck in the smaller places, like Antafagasta in Chile and Bueno-Ventura in Colombo, with the Oriental slums, small houses principally built of wood framing and completed with

corrugated iron or broken-up kerosene tins, which were eloquent testimony to the difficulties connected with the preservation of public health in such places. On the other hand, there were always one or more cinemas, however small and primitive, and I was reminded of the possibilities for public health propaganda which they might provide. If, for instance, films could be shown directed to instruction with regard to the prevention of malaria, cholera, typhoid and lesser diseases, it could do nothing but good and might prove invaluable. That this sort of propaganda is appreciated was suggested by the number of rather crude health posters which one saw displayed in various places. The consideration of this problem reminds me of the plan I saw in operation in Aden about three years ago. There the Port Sanitary Officer, Colonel Phipson, I.M.S., had a gramophone record made dealing with the simple measures that ought to be taken to prevent the various infective diseases which are liable to overrun such places with such tragic results. The record was produced in English, Arabic, Hindustani and Somali and was sold at a very cheap rate to the people, for many of the natives possess gramophones. The impression gained at a cinema may be vivid, but after all it is probably evanescent, and similar precise information which can be reiterated over and over again will surely make an appeal which, if not quite so graphic, may at least be looked on as of enormous supplemental value. I should like to suggest that the educational value of the cinema and the gramophone ought to be borne in mind by those who are concerned with health problems. The general observation suggested by the sort of tour with which I have dealt suggests the practical value of first-hand knowledge of the conditions existing in other countries. It certainly teaches one that physicians in other lands are only too anxious to be made familiar with the British point of view and are eager to discuss the facilities for the visitor from overseas who steps into Britain's medical circles. In Germany medical travel, at least for South Americans, is subsidized on every hand. There is the further advantage that the syllabus of the courses to be held is published long ahead, so that any one contemplating a visit will know what can be had in the way of lectures and demonstrations, perhaps six months before the time of the proposed visit. Since information about the activities of the medical institutions in Britain are not available in any one government or other central department, a foreigner is often at a loss to know to whom he is to apply for information, and the sooner we establish in London *one* really complete central bureau of medical information the sooner will this defect be rectified.

There is a great desire in South America for British publications, both books and periodicals, and for British drugs and instruments. The establishment of more scholarships in our medical schools and research

laboratories, such as those already endowed by the British Council, would also be welcome. Those who have already come over to England with university scholarships have suggested that the scope and details of the work to be done should be settled beforehand and that the student should receive help in mundane matters concerning the cost of travel, lodgings, etc. These things could best be arranged through a well regulated interchange of information, such as could be conducted through the suggested central bureau. One of the best of all methods for securing mutual advantage would be the interchange of assistants, and there one gathered that most of the difficulties would occur on our side in connection with the regulations of the General Medical Council. Attempts should continue to be made, however, to overcome these difficulties, because there is no doubt that the mutual advantage would be great. The student from South America who ardently desires to come to this country is not usually a man of means, and he can make the journey only at a considerable sacrifice either on his own part or the part of his parents, and they are anxious that such sacrifice should be made to the best advantage. Let me now say that the impression left by the British visitors who had preceded me was very vivid, and one heard much about Arbuthnot Lane, Lord Moynihan and Lord Dawson. Further, I should like to acknowledge gratefully the great assistance which I personally received from our Diplomatic Missions not only in the Argentine and in Chile, but in Uruguay, in the person of Mr. Millington-Drake, who does so much to promote international cultural relations.

PHYSIOLOGIC SPHINCTER OF HEPATIC BILE DUCT

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The purpose of this paper is to discuss the significance of cholangiograms obtained during operation which, in association with other circumstantial facts, prove the existence of a physiologic sphincter of the hepatic duct above the point of junction with the cystic duct.

PHYSIOLOGIC SPHINCTER

Contraction of the hepatic duct may be constantly observed cholangiographically during an operation. It takes place immediately above the crossing of the hepatic and cystic ducts and can be clearly seen when the walls of the ducts are elastic and thin. Neither total nor partial contraction is observable when the excretory passages are either dilated or thickened. In order to prevent artificial dilation of the biliary tract and any possible spasmodic reaction at the level of Oddi's sphincter, iodized poppyseed oil is injected at the rate of 1 cc. a minute to a total dose of 3 cc. in three minutes. Contraction is observable only when the iodized oil passes through the cystic duct slowly and in a small amount. If distention of the ducts occurs, as a result of a too large or a too rapidly injected dose, it is possible that the phenomenon cannot be seen even though an opaque substance more fluid than iodized poppyseed oil (such as colloidal thorium dioxide, skiodan or hippurate) is used. I intended to look at the hepatic duct during operation in a series of procedures in order to follow the behavior of the duct. However, I desisted from doing so because the structure is deeply situated, especially in obese, muscular patients like those on whom the operations were performed, and any maneuver at the hepatic hilus would have been dangerous: *"Primum non nocere."*

EXISTENCE OF TWO EXCRETORY SYSTEMS

The contractile mechanism of the hepatic bile duct functions when the gallbladder spontaneously empties itself. In the contractile phase the gallbladder–cystic duct–common bile duct system is the only one which can be visualized. The phenomenon is clearly seen if iodized oil is allowed to pass spontaneously from the gallbladder through the cystic duct into the common bile duct without any maneuver which may force passage of the substance to the bile ducts. A few minutes after injection

of the oil the substance fills the common bile duct, but it does not pass into the intrahepatic branches of the biliary tree. The phenomenon is also observable in animal experiments.

In 1 of the cholangiographic observations which were made during the operation, iodized poppyseed oil was injected into the gallbladder and forced to pass to the cystic duct by means of mild compression of the gallbladder. The opaque substance passed violently to the whole biliary tree; the ampulla of Vater was open, and the intrahepatic branches of the biliary tree as well as the hepatic and common bile ducts were

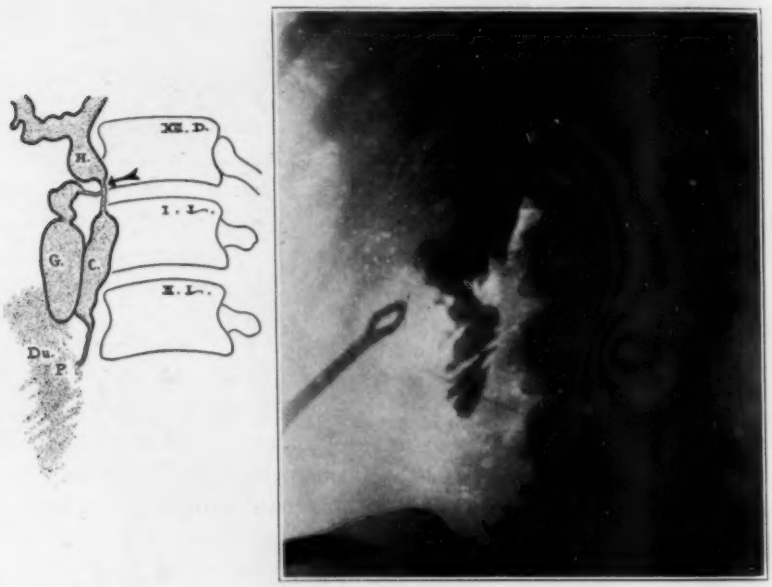

Fig. 1.—Cholangiography during operation. Iodized poppyseed oil was injected into the gallbladder (*G*). There was a strong contraction at the crossing. The intrahepatic bile ducts and the proximal segment of the hepatic duct (*H*) were filled with oil. The common bile duct (*C*), dilated to the volume of a little finger, easily emptied its contents into the duodenum (*Du*) through the papilla of Vater (*P*). (The patient was M. S., a woman aged 26. She was admitted to the hospital in April 1935. She had been operated on for chronic appendicitis at the age of 18 years. She had had the first hepatic colic one year previously, followed by subjaundice and urticaria. The crises were repeated. Operation was performed with the aid of spinal anesthesia. There was cholecystitis, without concretions. The structure contained stagnated bile.)

dilated. Contraction was restricted to the cysticohepatic–common bile duct crossing (fig. 1).

In the second clisé, taken ten minutes later, the intrahepatic branches were still filled with iodized oil, and the proximal segment of the hepatic

duct was dilated, whereas the terminal segment of the duct, near the crossing, was in a state of contraction. The gallbladder and the cystic and common bile ducts together formed a separate excretory system. The oil progressed slowly through the common bile duct, the diameter of which was greatly reduced. The substance was eliminated drop by drop through the papilla of Vater into the duodenum (fig. 2).

The relative independence of the two coordinated excretory systems was shown by a new series of roentgenograms, which showed active filling of the gallbladder by iodized poppyseed oil. I have observed several times that any resistance at the distal third of the common bile duct produces peristalsis of the duct for as long as it is tonic, by which

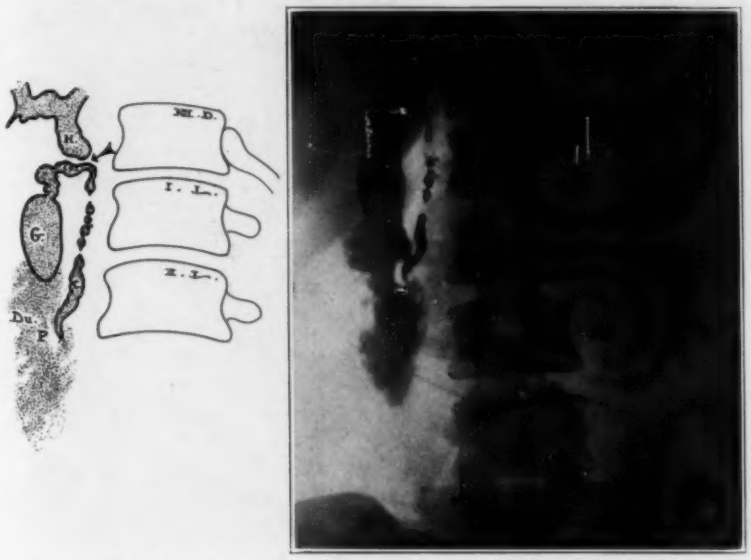

Fig. 2.—Cholangiography during operation. The roentgenogram was obtained ten minutes after the operation. The intrahepatic bile ducts and the proximal segment of the hepatic duct (*H*) were dilated, retaining all the iodized oil because of contraction of the distal portion of the hepatic duct (*H*). The gallbladder (*G*) made a system of evacuation with the common bile duct (*C*), the diameter of which was reduced to that of a quill. The oil was eliminated drop by drop through the papilla of Vater (*P*) into the duodenum (*Du*).

movement the column of oil ascends toward the crossing and drains into the cystic duct. The contraction of the hepatic duct prevents further progress of the opaque substance. This clearly shows the indirect protecting role of the hepatic duct, which favors repletion of the gallbladder with bile during the intervals of digestion (when the papilla of Vater is closed) as well as in any circumstance which changes the internal pressure of the common bile duct.

ABSENCE OF REFLUX OF OPAQUE SUBSTANCE BY PROPER DERIVATION OF SUBSTANCE

In general, when iodized poppyseed oil is directly injected either into the cystic duct or into the gallbladder itself, the upper branches of the biliary tract are partially injected with the substance. Notwithstanding the fact that the opaque substance progresses through the cystic duct slowly and regularly (as though it were being eliminated by the duct drop by drop) and independent of the mildness of the compression exerted on the gallbladder (when the substance is injected into the structure), a portion of the opaque substance overcomes the contraction

Fig. 3.—Cholangiography during operation. Iodized poppyseed oil was injected into the gallbladder (*G*). The opaque substance passed into the duodenum (*Du*) partially through the fistula which existed between the vestibule (*Vet*) and the duodenum (*Du*) and partially through the cystic duct (*Cys*), the common bile duct (*C*) and the papilla of Vater (*P*). The intrahepatic tree was not injected. The oil could not force its passage into the hepatic duct. (The patient was M. C., a woman aged 44, who was admitted in November 1936. The first hepatic colic had appeared twenty-five years previously, during the puerperium. Acute crises had appeared eleven years previously and had been repeated. During the last crises frequent vomiting had occurred and fever and jaundice had appeared. Operation was performed with the aid of spinal anesthesia. Acute pericholecystitis and a cholecystoduodenal fistula were present.)

of the hepatic duct and passes into the intrahepatic branches of the biliary tree. On the other hand, the opaque substance does not pass into the intrahepatic branches if a safety valve exists immediately adjacent

to the crossing point and counterbalances excessive pressure. I obtained this type of verification cholangiographically in patients who were operated on for a fistula. A communication was established between the neck of the gallbladder and the duodenal bulb by means of a small orifice similar to the urethral meatus of an adult. Ten cubic centimeters of iodized poppyseed oil was injected into the gallbladder. The structure was gently compressed in order to facilitate passage of the opaque substance into the biliary tree. A portion of the opaque substance passed to the duodenum through the fistula and another portion to the cystic duct–common bile duct system. The upper branches of the bilary tree

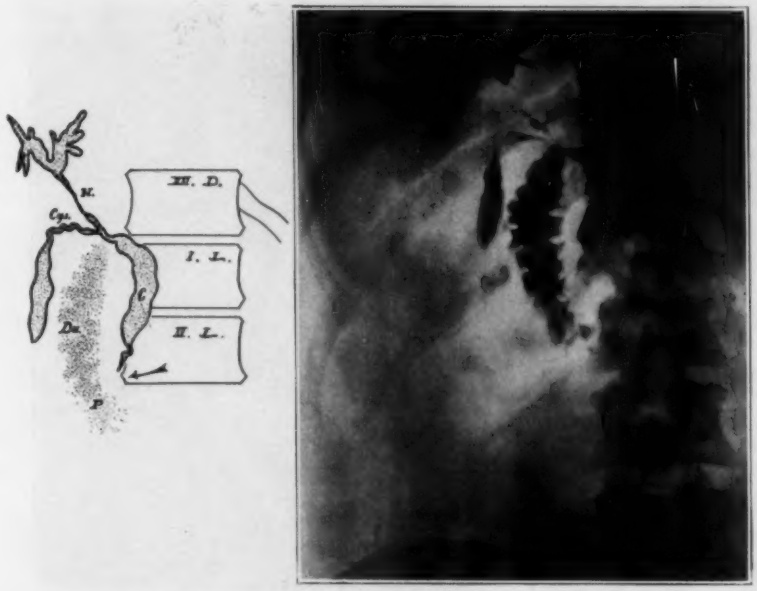

Fig. 4.—Cholangiography during operation (stenosing pancreatitis). Iodized poppyseed oil was injected through the cystic duct (*Cys*). The common bile duct, above the stricture, was moderately dilated and filled with oil. The hepatic duct (*H*) was contracted. A large amount of oil passed through the papilla of Vater (*P*) into the duodenum (*Du*). (The patient was R. P. de Z., an obese woman aged 38, who was admitted in March 1935. During the last eleven years she had been suffering from intermittent crises of pain in the epigastric region and the right hypochrondriac region. Sometimes the crises were followed by fever and jaundice. The zone of the pancreas and the common bile duct was painful on palpation. Operation was performed with the aid of spinal anesthesia. The calculous gallbladder was removed.)

were not invaded. There was sufficient contraction of the hepatic duct in this case to prevent the column of oil from ascending, and the excess passed through the fistula, which played a secondary neutralizing part (fig. 3). There is no other plausible explanation for the phenomenon.

The same phenomenon is observed when communication between the cystic duct and the duodenum is artificially established.[1] In the course of an operation I found the stump of a dilated cystic duct (improperly called neogallbladder). The operation was performed because of subintrant pain after cholecystectomy. Iodized poppyseed oil was injected into the stump (which was dilated to the size of an adult thumb). It showed the intrahepatic branches, which were dilated, the common bile duct, which was undulated from active peristalsis, and the presence of reflux in the duct of Wirsung. A laterolateral cysticoduodenostomy was made, after which a Petzer sound was left in the dilated stump.

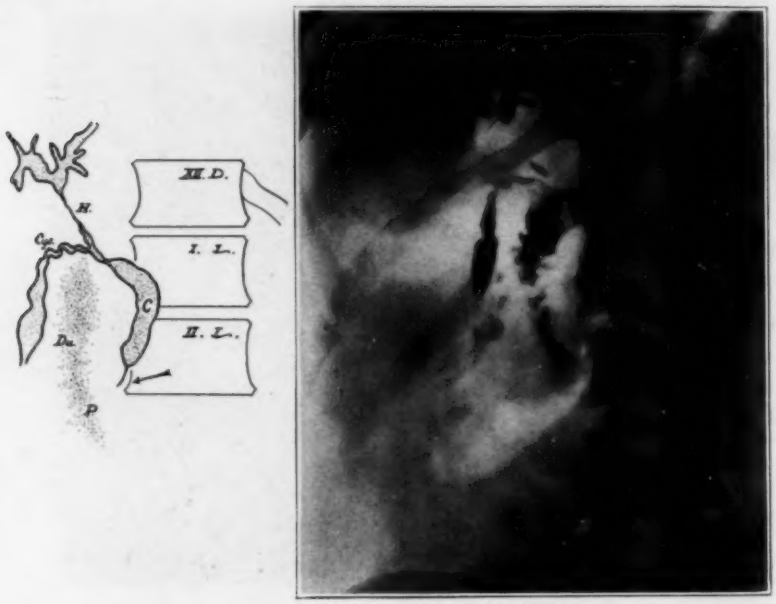

Fig. 5.—Cholangiography during operation. The roentgenogram was obtained fifteen minutes after the operation. The opaque substance in the common bile duct (*C*), which actively moved in peristalsis, was trying to subdue the obstacle. The filiform strictured zone is visible in the illustration.

Forty-eight hours later 10 cc. of the oil was injected through the sound into the stump, as had been done in the course of the operation. The clisé obtained during the injection did not show any reflux of the substance toward the upper branches of the biliary tree. The phenomenon proved once more that as soon as a neutralizing derivation of the excess either of pressure or of injected oil is established, the contractile mechanism of the hepatic duct begins to function.

1. Mirizzi, P. L.: Dyskinesie und Gallenblasenregeneration. Cystico-Duodenostomie, Deutsche Ztschr. f. Chir. **245**:156, 1935.

The common bile duct empties into the cystic duct when there is any resistance at its distal third. The phenomenon is frequently observed in the course of operations for calculous chronic cholecystitis when there is a stricture at the distal segment of the common bile duct near the papilla of Vater and the pancreatic duct in the absence of bile concretions. Figures 4 to 7 are explanatory. They show the picture in a case of stenosing pancreatitis following calculous cholecystitis in which cysticoduodenostomy was performed.

From these observations it is evident that contraction of the hepatic duct opposes progress of the opaque substance toward the intrahepatic

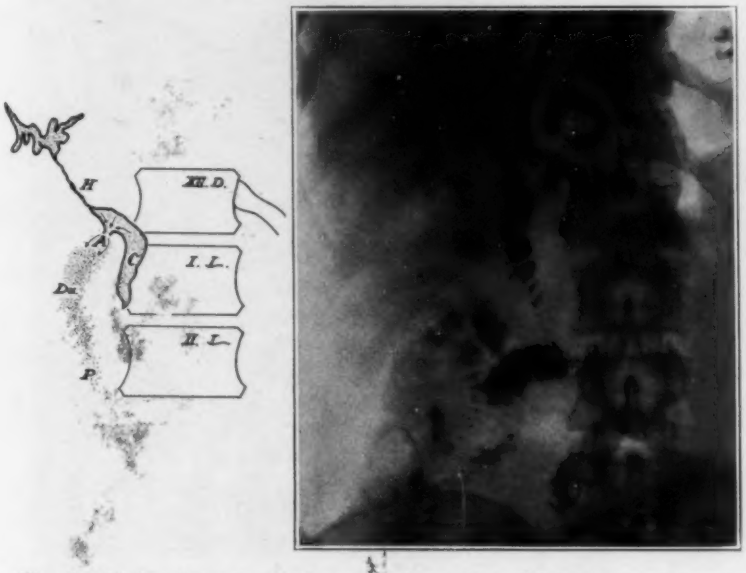

Fig. 6.—Cholangiography during operation. A cysticoduodenostomy was made. The transpancreatic segment of the common bile duct is not visible in the illustration. The main bile passage, between the point of contraction at the hepatic duct (*H*) and the stricture, at the level of the pancreas, was injected and in peristalsis. Iodized poppyseed oil passed through the anastomosis (*A*) into the duodenum (*Du*).

branches of the biliary tree, forcing the oil in the common bile duct to pass to the duodenum through the anastomosis. The phenomenon, which agrees with the normal physiology of the hepatic and common bile ducts, has been repeatedly verified by experimental proof of the existence of a contractile mechanism at the junction of the hepatic duct which plays a primary role in the excretion of bile. Section of the hepatic bile duct in biliary-intestinal anastomoses favors duodenal reflux. Certain technics of anastomosis (Alessandri), which make sectioning

of the anterior wall of the hepatic and common bile ducts necessary, seem improper because of the frequency with which reflux of the duodenal content through the anastomosis and toward the biliary tree establishes itself.[2]

In the only case in which I followed this technic (for derivation of the bile), duodenal regurgitation was observed. The same occurrence has been reported in the literature (Valdoni) with this type of anastomosis. Longitudinal section of the hepatic duct suppresses the defensive contraction of the duct and favors duodenobiliary regurgitation.

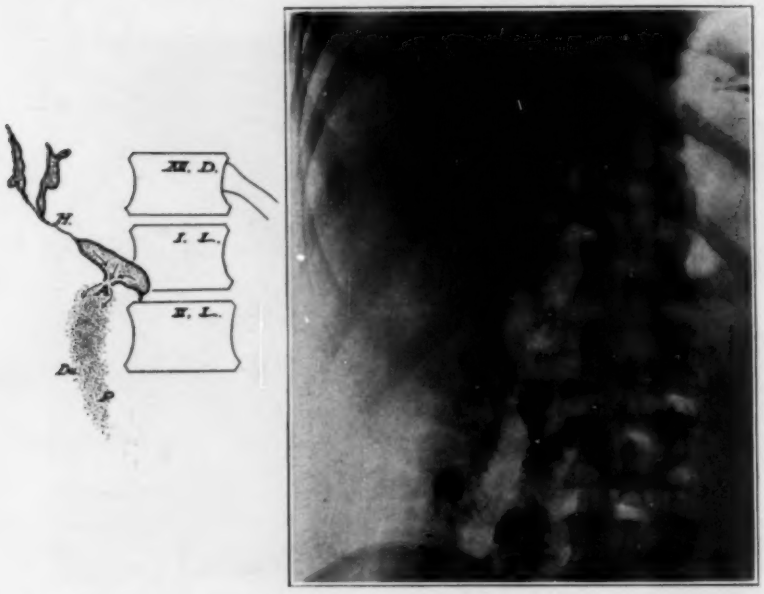

Fig. 7.—Cholangiography during operation. The roentgenogram was obtained sixty minutes after the operation. Iodized poppyseed oil accumulated at the distal part of the hepatic duct (*H*) and the proximal segment of the common bile duct opposite the anastomosis (*A*) through which the opaque substance passed into the duodenum (*Du*).

PRACTICAL CONCLUSIONS

Cholangiographic study during operation clarifies several direct and indirect facts which prove the existence of a physiologic, anatomic neurosympathetic center in the wall of the duct or in its proximity. The center controls the function of the hepatic bile duct in coordination with the distal segment of the common bile duct and the sphincter of Oddi.

2. Mirizzi, P. L.: L'infection ascendante dans les anastomoses bilio-digestives (àpropos d'une observation), Mém. Acad. de chir. **63**:907, 1937.

Because of these observations and from clinical experience I believe that integrity of the hepatic bile duct must be respected so as not to destroy contraction of the physiologic sphincter of the duct in creating a biliary-intestinal anastomosis. The same criterion compelled me to perform, systematically, low transverse choledochotomy in all cases of lithiasis of the common bile duct. In all cases, but especially in those in which contractility of the hepatic duct is evident, the operation is performed immediately on the upper edge of the duodenum.

LIGATION OF THE INFERIOR VENA CAVA

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AND
CHARLES HUGGINS, M.D.
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Sudden obstruction of the inferior vena cava above both kidneys has been found to be fatal in dogs, whereas ligation is well borne when carried out below the renal veins. A method is described whereby complete closure of the vena cava above both renal veins was successfully carried out.

Ligation of the inferior vena cava produces various effects, depending on factors which affect the adequacy of collateral circulation, namely, the site of ligation, suddenness of occlusion and species and age of the animal.[1] The site of ligation relative to the kidneys is of prime importance because of the enormous blood flow through the kidneys; it has been found that survival depends largely on the degree of compromise of the renal circulation.[2]

There is general agreement that ligation of the renal vein is followed by progressive atrophy of the kidney and decrease or complete cessation of all urinary secretion, invariably in cats [3] and rabbits [4] and nearly always in dogs.[5] Microscopic studies have shown that the damage is greatest in the tubules, the glomeruli being preserved relatively intact.[6]

Ligation of the vena cava just above the renal veins in the dog almost always results in death [7]; Polkey [2] had 1 of 5 dogs survive this

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From the Department of Surgery of the University of Chicago.

Aided by a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

1. *(a)* Pleasants, J. H.: Johns Hopkins Hosp. Rep. **16**:363, 1911. *(b)* Addis, T., and Lew, W.: Proc. Soc. Exper. Biol. & Med. **42**:602, 1939. *(c)* Montemartini, G.: Policlinico (sez. chir.) **41**:593, 1934.

2. Polkey, H. J.: Urol. & Cutan. Rev. **33**:294, 1929. Pleasants.[1a]

3. Zuckwer, J. T.: Am. J. Path. **2**:57, 1926.

4. Chin, R.: Tr. Jap. Path. Soc. **28**:277, 1938.

5. Harrington, S. W.: Effect on Kidney of Various Surgical Procedures on the Blood Supply, Capsule, and on Ureters, Arch. Surg. **2**:547 (May) 1921.

6. Bender, J. A., and Hayman, J. M., Jr.: Proc. Soc. Exper. Biol. & Med. **32**: 1018, 1935.

7. Zuckwer.[3] Pleasants.[1a] Montemartini.[1c]

ligation. In the rat, however, similar ligation in young animals causes only a transient period of renal insufficiency followed by complete recovery in almost all cases; the mortality rate from the procedure was found to increase with the age of the rats.[1b]

Abundant evidence exists that ligation of the vena cava below the renal veins is not a serious surgical procedure either in man or in the lower animals.[2] Edema or slight albuminuria may develop, but neither is common.

In this study, the venous drainage of one kidney was impeded, and we were interested in (*a*) the functional changes which occurred due to this venous obstruction, (*b*) the compensatory changes which resulted in the unobstructed kidney and (*c*) the possibility of ligating the vena cava subsequently above both renal veins.

METHODS

Female dogs kept under standard laboratory conditions were used in all experiments; all operations were performed with ether anesthesia and with aseptic technic. The animals were first prepared by transplanting the ureters with a small cuff of bladder into the skin of the corresponding groin fold. When ready for experimentation the dog was placed on its back on a table, and urine was allowed to collect in the natural anatomic pocket of each groin. Little restraint was usually necessary; the dogs were kept comfortable by frequent rest periods. The urine was removed by pipets, the method making possible quantitative collection of the secretion from each kidney without the use of catheters and experimentation on one kidney with the other reserved as a control. Before each observation period food was withheld for eighteen hours; water was given freely one hour before the collection of urine to insure adequate urine flow. It was interesting to note that fright or other distress caused almost immediate cessation of urine flow, sometimes for a minute or more. An ammoniacal dermatitis developed in a few dogs but was usually temporary.

Oblique inter-renal ligation consisted in placing a silk ligature diagonally around the vena cava in such a way (fig. 1) that one renal vein was drained above it and the other below, free communication remaining between each renal vein and the adjoining vena cava. After ligation venous pressures were measured in the veins of the leg with a saline manometer connected to a needle in the vein as a direct method. In an acute experiment it was found that pressure in the veins of the leg closely reflected pressure in the obstructed vena cava below the ligature. Arterial pressures were measured directly in the femoral vessels, without anesthesia, by a mercury manometer.

Renal function was studied by creatinine and phenol red clearances, rate of excretion of phenol red and measurement of volume and total solids. It is well established that the exogenous creatinine clearance is a measure of glomerular filtration in the normal dog kidney.[8] Sterile solutions of creatinine in doses large enough (usually 200 mg. per kilogram) to elevate the blood plasma level to 10 to

8. Smith, H. W.: The Physiology of the Kidney, New York, Oxford University Press, 1937, p. 96.

20 mg. per hundred cubic centimeters were given subcutaneously. One hour later, when the blood level had became more or less stable, clearances were started. Urine was collected for periods of ten minutes with rest intervals between. Samples of venous blood were taken at the middle of each period or interpolations made to that point. The syringe was moistened with a drop of saturated potassium oxalate, and the blood was gently transferred to a tube containing another drop of oxalate. Creatinine determinations were made according to a slight modification of Folin's alkaline picrate method [9] on diluted urine and on plasma from which the proteins had been precipitated by tungstate, with use of the Evelyn photoelectric colorimeter (Wratten filter no. 75 + 9785), and all clearances were calculated as plasma clearances. Accuracy of the method was checked by recovery from blood of known amounts of creatinine which had been added. Urine flow in our experiments was

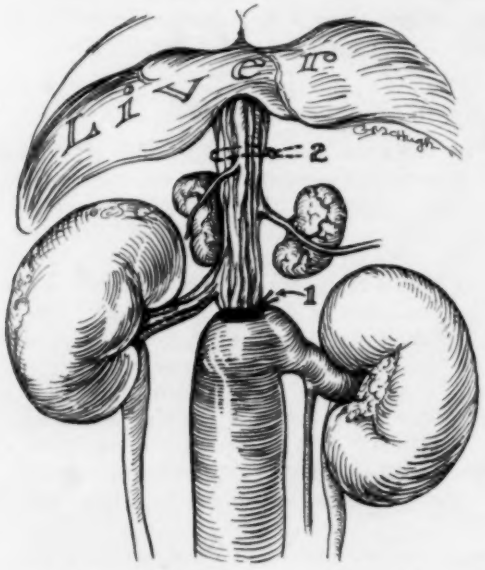

Fig. 1.—Oblique inter-renal ligation of the inferior vena cava. A ligature is so placed *(1)* that one renal vein drains below the ligature while the other drains above it. Subsequently high ligation of the vena cava *(2)* can be carried out successfully.

sometimes as low as 0.1 cc. per minute from one kidney, but Shannon [10] has shown that the creatinine clearance is independent of urine flow, even at very low levels of flow.

Tubular action was studied by the rate of excretion of phenol red and by phenol red clearances done simultaneously with creatinine clearances. Just before the creatinine clearances were started, a single injection of alkaline phenol red was given intravenously in amounts sufficient to raise the plasma level initially to 3 to 6 mg. per hundred cubic centimeters; clearances were done on the falling blood level.

9. Folin, O., and Wu, H.: J. Biol. Chem. **38**:98, 1919.

10. Shannon, J. A.: Am. J. Physiol. **114**:362, 1936; Proc. Soc. Exper. Biol. & Med. **33**:474, 1935.

Since phenol red interferes with the colorimetric determination of creatinine, a special logarithmic graph (fig. 2) was made to show compensation for interference at various concentrations of phenol red. The phenol red content of the plasma was determined by alkalinizing the plasma diluted with saline solution to the appropriate concentration and reading in the Evelyn colorimeter with filter 540, using a blank of diluted plasma taken before the injection of dye. Hemolysis was infrequently obtained. No attempt was made to differentiate the glomerular filtration fraction of the plasma phenol red clearance.

The rate of excretion of phenol red was measured after intravenous injection of 6 mg. of the dye; urine was collected for two fifteen minute periods. Urine was examined microscopically and tested for albumin occasionally. Total solids were determined by accurately weighing 1 cc. of urine before and after drying at 105 C. overnight.

RESULTS

A. *Ligation of the Vena Cava Above Both Renal Veins.*—Two dogs in which the vena cava was tied above both renal veins died in shock five and ten hours respectively after operation. In the leg the venous pressure was 26 cm. of water in

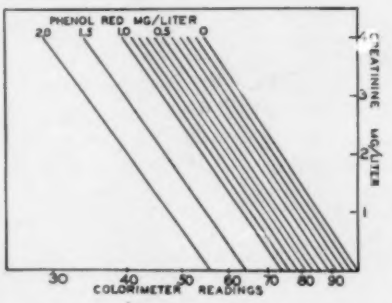

Fig. 2.—Semilogarithmic graph for determination of creatinine in the presence of phenol red.

1 dog; the rectal temperature was 98.6 F.; the body surfaces were cold, and the skin was cyanotic over the lower half of the body. At autopsy the kidneys were tense and dark red; the vessels of the lower half of the body were engorged, and the soft tissue was edematous and mottled in places with petechial hemorrhages. In both dogs small amounts of dark, bloody urine were observed in the bladder.

B. *Ligation of One Renal Vein.*—A renal vein was ligated in each of 2 dogs; in 1 the obstructed kidney within two hours was secreting only a small amount of coagulated and fibrinous pale pink urine. The urine the next day was clear in the gross but continued to be minute in amount and very dilute. It contained many epithelial cells. In two months there was no sign of recovery. The obstructed kidney in a second dog was at first putting out small amounts of visibly bloody urine but recovered rapidly until, at the end of two weeks, it was functionally equal to its mate. Compensatory hypertrophy of the normal kidney was marked in both dogs, persisting in the first and disappearing in the second dog as the damaged kidney returned to normal. For changes in creatinine clearance in the second dog, see figure 3.

C. *Oblique Inter-Renal Ligation of the Vena Cava.*—Inter-renal ligation was performed in 5 dogs (fig. 1). Invariably the immediate result was almost complete suppression of urine on the obstructed side, with a consequent drop almost to zero of all clearances and of phenol red excretion. Albumin and gross blood appeared in the urine of the obstructed kidney in all dogs, decreasing markedly after a day or two. In 4 of the dogs recovery of the obstructed kidney began promptly and progressed steadily until (within three to six weeks) function was fairly good, although it never equaled that of the normal kidney. Small amounts of albumin and a few red and white blood cells could constantly be found in the urine, which was dilute, total solids being approximately one-fourth normal (fig. 4). Intravenous administration of physiologic solution of sodium chloride produced

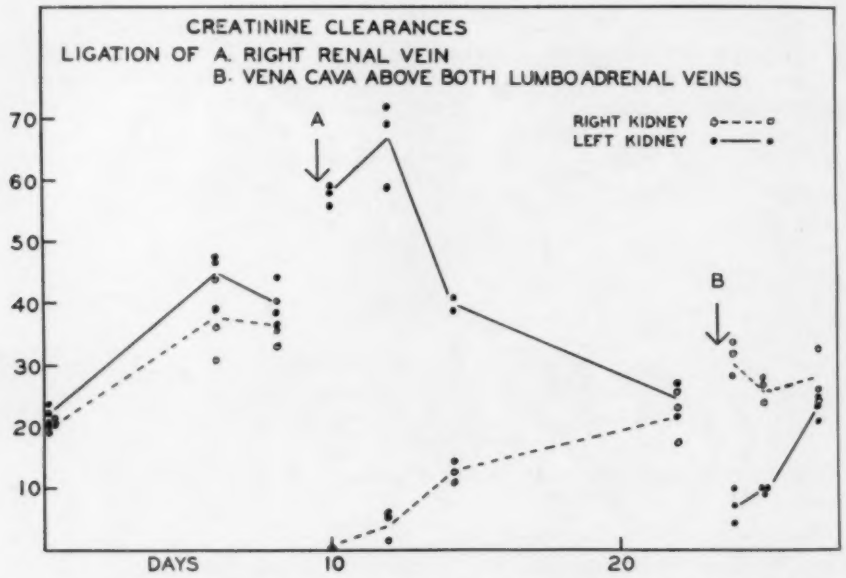

Fig. 3.—Changes in creatinine clearances after ligation of the right renal vein and of the vena cava above both renal veins fifteen days later. Three clearances were done at each test. Note the increase in function of the normal kidney and the depression and recovery of the obstructed kidney. The ordinate units are cubic centimeters per minute; the abscissa is time in days.

marked increases of volume secreted by the damaged kidney without altering clearance values.

In 1 dog, however, no recovery occurred in the damaged kidney throughout thirteen and one-half weeks of observation. A very slight increase in function occurred when the opposite, normal kidney was removed.

Concurrently with depression of the kidney obstructed by oblique ligation was a uniform increase in function of the unobstructed kidney. Increase in all clearance values and volume output appeared within two to three hours after ligation. The following day values were usually less, but thereafter they increased daily for approximately two weeks, not much difference being observed between increases in

phenol red and creatinine clearance values. In the dogs in which recovery of the injured kidney occurred, the functional hypertrophy decreased synchronously with the increase on the recovering side (fig. 5).

D. *Ligation of the Vena Cava Above Both Renal Veins Subsequent to Oblique Inter-renal or Renal Vein Ligation.*—Ligation of the vena cava above both renal

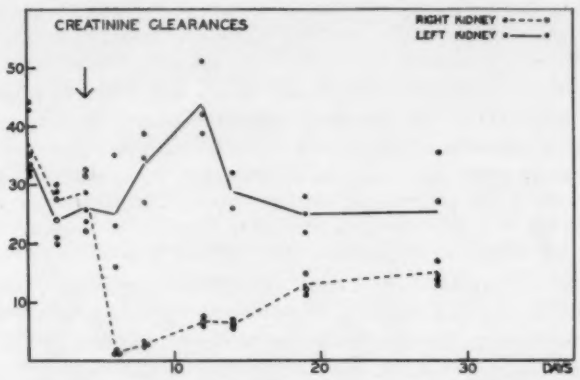

Fig. 4.—Changes in creatinine clearances after oblique inter-renal ligation of the vena cava above the right renal vein. The ordinate units are cubic centimeters per minute; the abscissa is time in days. Note the depression of the obstructed kidney, followed by progressive recovery; the compensatory increase in function of the normal kidney decreased with return of function of the other kidney.

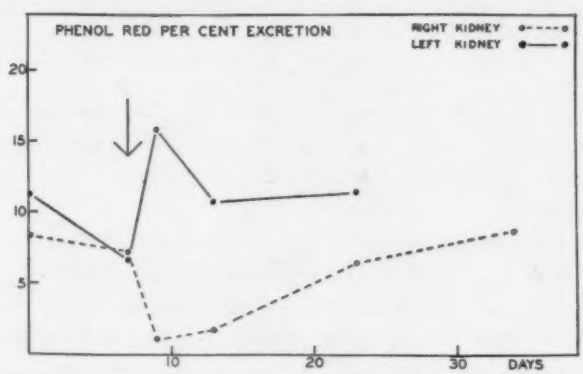

Fig. 5.—Changes in phenol red excretion after oblique inter-renal ligation of the vena cava above the right renal vein. The ordinate is the percentage of 6 mg. of phenol red eliminated within thirty minutes of initial venous injection. The abscissa is time in days. Complete recovery occurred in the obstructed kidney.

veins was performed in 2 dogs after inter-renal ligation and in 2 dogs after ligation of one renal vein. In no case was the procedure fatal, resulting only in relatively mild depression of the normal kidney and extrarenal symptoms, which will be mentioned later. Complete recovery of the slightly damaged kidney occurred.

E. *Extrarenal Effects of Ligation of the Vena Cava.*—Ligations at the sites mentioned produced prompt cyanosis of the lower half of the body in all animals, accompanied by dilatation of small veins in the skin, elevated venous pressure and usually slight edema. The cyanosis regularly disappeared within twenty-four hours and the edema within three or four days. Progressive enlargement and tortuosity of the larger cutaneous veins were the only permanent signs of obstruction. Elevation of venous pressure in the hindlimbs was 25 to 40 cm. of water, compared with 5 to 10 cm. in the forelimbs; decrease in pressure occurred until normal values were reached, usually within a week. The arterial pressures were all normal.

F. *Hypertrophy in an Explanted Kidney.*—In a dog with one kidney explanted by Alving's method [11] it was possible to observe changes in size resulting from compensatory hypertrophy and ligation of the vena cava. After ligation of the renal vein one kidney became practically functionless, but the explanted kidney did not increase in size, although its function as measured by clearances was steadily increasing. Ligation of the vena cava above both renal veins caused a slight enlargement, which had entirely disappeared within eighteen hours.

G. *Autopsy Observations.*—In 3 dogs with oblique inter-renal ligation and in 1 with ligation of a renal vein followed by ligation of the vena cava, autopsy revealed complete obliteration of the vena cava below the ligature, only a fibrous cord marking the course of the vessel; the obstructed renal vein in each case was completely fibrosed. In 1 dog with oblique inter-renal ligation of the vena cava and one with ligation of the renal vein followed by ligation of the vena cava the cava was patent both above and below the ligature, which was intact, although the obstructed renal veins were thrombosed. Collateral channels involved chiefly anastomoses of capsular veins with lumbar, lumboadrenal and ovarian veins and the vena cava when that vessel remained patent. One kidney which had no return of function was very small, weighing only 10 Gm.; it was pale and firm, without dilated capsular veins. Otherwise gross and microscopic studies of the kidneys were noncontributory.

COMMENT

It had been intended to study excretory tubular mass and renal blood flow in obstructed kidneys, but renal damage was found to be so gross that it was useless to apply the finer discriminations in the use of clearances to determine those points.

Our results confirm those of Montemartini,[1c] Polkey [2] and others, who have found that ligation of the vena cava above both renal veins is nearly always fatal. We cannot draw conclusions from two complete ligations of the renal vein, but one of them resulted in excellent recovery of renal function.

Inter-renal ligation produces, at least for a period before thrombosis occurs, acute passive congestion of the kidney similar to that produced by Rowntree, Fitz and Geraghty [12] by partial occlusion of venous drainage. They found that slight constriction of a renal vein sometimes

11. Gorden, W.; Alving, A. S.; Kretzschmar, N. R., and Alpert, L.: Am. J. Physiol. **119**:483, 1937.

12. Rowntree, L. G.; Fitz, R., and Geraghty, J. T.: The Effects of Experimental Chronic Passive Congestion on Renal Function, Arch. Int. Med. **11**:121 (Feb.) 1913.

produced mild polyuria; in our experiments passive congestion, although probably more severe than theirs, has always produced oliguria, amounting at times almost to anuria. Toth,[13] by having animals breathe oxygen at low tension, has shown that oliguria usually results from anoxia in anesthetized dogs, whereas polyuria is the usual response in unanesthetized ones. Winton,[14] in the heart-lung-kidney preparation, demonstrated that a rise in renal venous pressure to 20 mm. of mercury decreased the output of urine 30 per cent. Schmidt and Chen [15] elevated intra-abdominal pressure to 27 to 28 mm. of mercury and found that urine flow stopped unless a glass cannula was inserted into the renal vein. They, as well as Winton,[16] found that saline diuresis easily overcame these pressures. Lasher and Glenn,[17] who anastomosed the renal artery and vein, found cessation of urinary flow.

Studies of explanted kidneys are of value in studying the problems of compensatory hypertrophy. Moberg,[18] using rats, found evidence that anatomic hypertrophy may occur independently of functional hypertrophy and that degenerative changes always occurred in hypertrophied tubules. MacKay, Addis and MacKay,[19] Allen [20] and others have shown that a high protein diet increases anatomic hypertrophy. Mason, Blalock and Harrison,[21] using their direct method of measuring blood flow from the two renal veins, found that unilateral nephrectomy caused a 30 per cent decrease in blood flow.

Our observations revealed an immediate marked increase in the measurements of function of the normal kidney, in glomerular filtration as well as tubular activity. That this increase represents opening up of unused nephrons is doubtful, in view of White's evidence that all glomeruli of the dog function simultaneously.[22] Compensatory hypertrophy, beginning promptly, increased steadily for about two weeks before leveling off except in dogs in which the damaged kidney recovered. The explanted kidney of 1 dog did not increase in size while

13. Toth, L. A.: Am. J. Physiol. **119**:127, 1937.

14. Winton, F. R.: J. Physiol. **72**:49, 1931.

15. Schmidt, C. F., and Chen, K. K.: Proc. Soc. Exper. Biol. & Med. **21**:414, 1923.

16. Winton, F. R.: Physiol. Rev. **17**:408, 1937.

17. Lasher, E. P., Jr., and Glenn, F.: Effects on Kidney and Blood Pressure of Artificial Communication Between Renal Artery and Vein, Arch. Surg. **38**:886 (May) 1939.

18. Moberg, E.: Acta path. et microbiol. Scandinav., 1936, supp. 31, p. 1.

19. MacKay, L. L.; Addis, T., and MacKay, E. M.: J. Exper. Med. **67**:515, 1938.

20. Allen, R. B.: J. Urol. **34**:553, 1935.

21. Mason, M. F.; Blalock, A., and Harrison, T. R.: Am. J. Physiol. **118**:739, 1937.

22. White, H. L.: Proc. Soc. Exper. Biol. & Med. **41**:190, 1939.

undergoing functional hypertrophy. Soskin and Saphir [23] have reported that prevention of anatomic hypertrophy by imprisoning the kidney in a cast was fatal to unilaterally nephrectomized animals.

In spite of interference with venous drainage, no hypertension was observed in any of our dogs. This observation confirms those of Eichelberger [24] on hydronephrosis, contrasting with those of Katz and his co-workers.[25] Bell and Pederson [26] found that hypertension lasting several months regularly developed in rabbits in which a renal vein was almost completely occluded and collateral circulation was not permitted to develop.

SUMMARY

Individual renal function was studied in dogs with cutaneous ureterostomies, by means of creatinine and phenol red clearances. Remarkable parallelism amounting almost to equality of function exists in the paired normal kidneys.

Ligation of the vena cava above both renal veins in 2 normal dogs produced surgical shock which was fatal in five and ten hours respectively.

In 5 dogs oblique inter-renal ligation of the vena cava was performed, one renal vein being included below the ligature, causing venous congestion in the corresponding kidney, while venous drainage from the opposite kidney was unimpaired. In all dogs there was immediate depression of function on the obstructed side; in 4 of the 5 eventual functional recovery was almost complete, and in the fifth no recovery occurred. Coincident with the depression on the obstructed side, there was marked functional hypertrophy on the normal side; this increase persisted as long as the other kidney was damaged and disappeared if and when function of the other returned. These dogs survived subsequent ligation of the vena cava above both renal veins, and the operation produced minimal effects on the kidneys.

Complete ligation of the main renal vein in 1 dog resulted in functional depression with recovery of the kidney in thirteen days, while in another dog permanent impairment resulted. In each dog subsequent ligation of the vena cava above both renal veins was well tolerated.

Measurements of an explanted kidney undergoing hypertrophy showed that functional hypertrophy may occur without commensurate anatomic hypertrophy.

Autopsy studies showed that the recovery of renal function after venous obstruction depends on the development of an adequate collateral

23. Soskin, S., and Saphir, O.: Am. J. Physiol. **101**:573, 1932.

24. Eichelberger, L.: Proc. Soc. Exper. Biol. & Med. **42**:249, 1939.

25. Megibow, R. S.; Friedberg, L.; Rodbard, S., and Katz, L. N.: Proc. Soc. Exper. Biol. & Med. **43**:245, 1940.

26. Bell, E. T., and Pederson, A. H.: Ann. Int. Med. **4**:227, 1930.

renal venous drainage. Allowing time for development of collateral circulation to one kidney made possible high ligation of the vena cava in dogs.

CONCLUSIONS

Ligation of the vena cava above both renal veins causes death in dogs in a few hours from surgical shock due to accumulation of blood from two kidneys, in the posterior portion of the body. When oblique ligation of the vena cava between the kidneys is done, allowing development of collateral veins in one kidney, subsequent complete high ligation of the vena cava is well borne; it is not followed by shock or interference with renal function in the kidney with adequate venous drainage.

SICKLE CELL DISEASE

PATHOGENIC, CLINICAL AND THERAPEUTIC CONSIDERATIONS

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LOS ANGELES

Since the original description of sickle cell anemia by Herrick in 1910,[1] sufficient data have been accumulated to permit certain statements concerning the pathologic physiology involved and to warrant certain practical conclusions as to the management of the condition. The purpose of this contribution is to put on record additional data derived from personally studied material, as well as additional conclusions, chiefly therapeutic, derived from these data and from other data already on record in the literature.

It was striking to observe, in the material examined, that:

1. Sickle cell anemia is not infrequently entirely overlooked by the clinician and is discovered only by the pathologist at necropsy. The diagnosis is established by the observation of a small, markedly atrophied spleen, which consists merely of a mass of partially calcified fibrotic tissue. This type of spleen is unknown in any other diseases except those in which complete destruction of the splenic blood supply has occurred.

2. Errors of diagnosis are not infrequent. The enlarged heart, systolic murmur and accentuated second pulmonic sound observed in the patient with sickle cell anemia may lead to an incorrect diagnosis of rheumatic mitral lesion. Sickle cell anemia may account for hypertrophy of the right side of the heart without a valvular lesion. It may be the underlying cause of ulcers of the leg. It may give rise to pains, presumably of rheumatic origin, in the muscles, bones and joints. It may also cause so-called abdominal crises which may be diagnosed as acute appendicitis or perforated peptic ulcer and for which operation may be done unnecessarily or even with fatal consequences.

3. Patients with sickle cell anemia present very poor medical and surgical risks. They may succumb to such a relatively simple disease as acute catarrhal colitis. They may lose their lives from such a simple

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1. Mason, V. R.: Sickle-Cell Anemia, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 3, p. 2329.

procedure as appendectomy or hernioplasty because their disease was not recognized and they were not properly protected against the risk inherent in it. They may die after a blood transfusion correctly done with compatible blood.

NATURE OF THE SICKLE CELL TRAIT (SICKLEMIA)

Sickle cell anemia is one of several recognized types of inborn, hereditary (constitutional) abnormalities of the red blood corpuscles, including, in addition, constitutional hemolytic jaundice (Minkowski-Chauffard); ovalocytosis (Dresbach); and Mediterranean erythroblastic anemia (Cooley's disease).

Certain facts concerning the sickling phenomenon are now clearly established.[2] Sickling is dependent solely on the red blood cells. It does not depend on any peculiarity of the plasma. It is readily demonstrated by a simple laboratory technic. It is markedly enhanced both in vitro and in vivo by lack of oxygen and by an increased supply of carbon dioxide.[3] The phenomenon is reversible, and exposure of the sickle cells to an atmosphere rich in oxygen permits them to resume their spherical form. Sickling undoubtedly occurs in the circulating blood and may be seen even in immature nucleated red cells. Because the sedimentation velocity of the affected cells is diminished, the sedimentation rate may be normal even in the presence of marked anemia.[4] Sickling cells do not show any rouleau formation.[4a] They are definitely more resistant to hypotonic salt solution than are normal red blood cells, and in some persons some sickle cells do not exhibit hemolysis even in distilled water.

Several important facts concerning the sickling phenomenon are still unknown. Thus it is not possible to say at this time whether the filaments produced by normal living red corpuscles are the agents which cause the sickling deformation of certain erythrocytes (Auer[5]). It is not known what kind of peculiar and specific "surface phenomenon"[6] is the operative factor. Finally, investigations on the electric charges of sickling cells, which may offer a clue for elucidation of the problem, have not yet been carried out.

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2. (*a*) Diggs, L. W., and Bibb, J.: The Erythrocyte in Sickle Cell Anemia, J. A. M. A. **112**:695 (Feb. 25) 1939. (*b*) Mason.[1]

3. Hahn, E. V., and Gillespie, E. B.: Sickle Cell Anemia, Arch. Int. Med. **39**:233 (Feb.) 1927. Scriver, J. B., and Waugh, T. R.: Studies on Case of Sickle Cell Anemia, Canad. M. A. J. **23**:375, 1930.

4. (*a*) Bunting, H.: Sedimentation Rates of Sickled and Non-Sickled Cells from Patients with Sickle Cell Anemia, Am. J. M. Sc. **198**:191, 1939. (*b*) Diggs and Bibb.[2a]

5. Auer, J.: Structure and Function of Filaments Produced by Living Red Corpuscles, Am. J. M. Sc. **186**:776, 1933.

6. Huck, J. G.: Sickle Cell Anemia, Bull. Johns Hopkins Hosp. **34**:335, 1923.

It may be accepted as an established fact that sicklemia is due to an inborn and constitutional abnormality of erythropoiesis. The essential abnormality is that variable numbers of red cells are produced which exhibit characteristic deformities under conditions which do not alter normal red cells (Mason). The constitutional sickle cell trait is transmitted by heredity as a dominant mendelian characteristic (Huck[6]). That the trait is not recessive is demonstrated by an observation of King and Janeway:[7] In a family in which both parents were affected, only four of the six children inherited sicklemia, whereas a recessive characteristic would have been transmitted to all six children.

If sickle cell disease, as will be pointed out later, is due to the deleterious consequences resulting from the abnormal constitutional trait sicklemia, one might expect to find other constitutional abnormalities rather frequently in persons affected with it as compared with normal persons. This is not the time to consider whether the sickle cell trait represents one of the degenerative stigmas characterizing what I[8] have termed "status degenerativus," but certain suggestive evidence might be briefly listed here:

1. A 10 year old Negress who died of massive necrosis of the renal cortex due to impaction of sickled cells in the small renal vessels also presented a thyroglossal cyst and multiple congenital cysts and abnormal fissures in the lungs.

2. A 4 year old Negro child who succumbed unexpectedly to simple catarrhal colitis exhibited at autopsy sickle cell disease and feminine pseudohermaphroditism. The child had been brought up as a boy, and hypoplasia of the penis and a mild degree of hypospadias had been diagnosed ante mortem. Autopsy revealed female internal genital organs, a communication between the vagina and the urethra and an absence of testicular tissue.

3. A 70 year old Negress with sickle cell anemia presented at postmortem examination an atrophic spleen weighing 16 Gm. and multiple leiomyomas of the stomach.

4. Somewhat similar observations are on record in the literature. Ryerson and Terplan[9] described in 1 of their cases "a tendon-like thickening . . . of the lower part of the right aortic valve, apparently

7. King, J. T., and Janeway, C. A.: Sickle Cell Anemia with Cardiac Complications, Internat. Clin. **3**:41, 1937.

8. Bauer, J.: Vorlesungen ueber allgemeine Konstitutions- und Vererbungslehre, ed. 2, Berlin, Julius Springer, 1923; Konstitutionelle Disposition zu inneren Krankheiten, ed. 3, Berlin, Julius Springer, 1924.

9. Ryerson, C. S., and Terplan, K. L.: Sickle Cell Anemia: Two Unusual Cases with Autopsy, Folia haemat. **53**:353, 1935.

corresponding to an abnormal fibre of the specific bundle." Harden [10] reported oxycephaly and congenital abnormalities of the retinal blood vessels in 2 brothers affected with sickle cell anemia. Haden and Evans,[11] in reporting hereditary "flexion deformity of the little finger" (camptodactylism) in 2 sisters of Sicilian descent with sickle cell anemia, wrote: "The familial occurrence of the flexion deformity of the finger in this family is of great interest, since s.c.a. is considered a similar anatomic defect in the shape of the erythrocyte." It is not inconceivable that persons with such crooked fingers may also have other "crooked" structures and functions, though I am not inclined to accept the word as literally as these authors did. It must be noted, however,[12] that crooked little fingers were first described by Adams in 1890 and that Landouzy, who first applied the term camptodactylism to the deformity,[12] considered it a constitutional stigma.

It should be emphasized that the observations which have been cited are merely suggestive and are not put forward as evidence of an association of sickle cell anemia with other constitutional stigmas.

PATHOGENESIS OF SICKLE CELL ANEMIA

That sickle cell anemia is hemolytic (produced by an exaggerated destruction of red blood corpuscles) is capable of clinical and anatomic proof. Clinical proof is supplied by the acholuric jaundice which regularly accompanies it; the indirect van den Bergh reaction in the blood serum; the increased output of urobilin in the urine and in the stools, and such signs of stimulated erythropoiesis as an increase in the number of reticulocytes and nucleated red cells. Anatomic proof of the increased destruction of red blood cells is supplied by the evidences of increased activity of the reticuloendothelial system in the spleen, the liver, the bone marrow and the lymph nodes; proliferation of the Kupffer cells, which occasionally show marked phagocytosis of the erythrocytes, and large deposits of hemosiderin found in various organs.

The mechanism of the destruction of blood associated with sickle cell anemia is still unknown, but it seems clear that it differs from that of the abnormal hemolysis of hemolytic jaundice. In the latter disease the probable operative factors are the increased fragility of the spherocytes and the increased activity of the spleen. In the presence of sickle cell anemia, on the contrary, the red cells are even less fragile than normal

10. Harden, A. S.: Sickle Cell Anemia, Am. J. Dis. Child. **54**:1045 (Nov.) 1937.

11. Haden, R. L., and Evans, F. D.: Sickle Cell Anemia in the White Race, Arch. Int. Med. **60**:133 (July) 1937.

12. Aschner, B., and Engelmann, G.: Konstitutionspathologie in der Orthopaedie, Berlin, Julius Springer, 1928.

ones, and in cases of the advanced condition the spleen seems almost completely exhausted and its functional capacity practically lost. The anemia, nevertheless, may become severe.

As a matter of fact, both Cooley's anemia and the anemia due to ovalocytosis are also hemolytic. The osmotic resistance is increased in the former condition and is at least not diminished in the latter. Furthermore, it must be remembered that even in cases of hemolytic jaundice the destruction of the blood in the body is not caused by exposure of the erythrocytes to hypotonic solutions. An increased osmotic fragility merely indicates that the red corpuscles possess a faulty structure or an abnormal composition. It has long been known that the resistance of red blood cells varies with different agents and under different circumstances. The resistance toward lysolecithin of the red cells has been found increased in some cases of sickle cell anemia, which is in contrast to the diminished resistance observed in cases of constitutional hemolytic jaundice (Singer [13]). In the presence of sickle cell anemia the erythrocytes have been shown to have a somewhat diminished resistance to mechanical trauma as compared with normal controls.[2a] On the other hand, their demonstration in the circulating blood twenty-one days after they had been transfused into normal persons (Sydenstricker) would seem to indicate,[1] even though reliable normal control studies are not available,[14] that they are not liable to premature destruction.

Mason [1] assumed that in cases of sickle cell anemia the mode of disintegration of the red cells may be active phagocytosis of defective erythrocytes by macrophages, with liberation of hemoglobin. Such a hypothesis is scarcely in accord with his own statement that there is "no evidence of perverted activity of phagocytes in the disease."

On the basis of both clinical observations and histologic studies, I am convinced that the extensive hemolysis which accompanies sickle cell anemia is due to a relatively simple process. It is caused by the mechanical impaction of masses of deformed red blood cells in the smaller blood vessels of various organs. This impaction, with the subsequent hemolysis of the resulting conglutinated masses, is responsible for the further pathologic changes and for the clinical symptoms of sickle cell anemia.

The massive hemolysis associated with sickle cell anemia can reasonably be explained on a morphologic basis. The most striking feature of the disease is the engorgement of small blood vessels with

13. Singer, K.: The Lysolecithin Fragility Test, Am. J. M. Sc. **199**:466, 1940.

14. Dekker, H. J. N.: The Fate of the Transfused Red Blood Cells, Acta med. Scandinav. **99**:587, 1939.

sickled red corpuscles. The liver and, in the initial stages, the spleen are most frequently affected. The sinusoids of the spleen are for the most part compressed and relatively empty, and the pulp is engorged with masses of erythrocytes, which are greatly elongated, pointed, curved and bizarrely shaped. Sometimes the capillaries of the malpighian bodies are enlarged and appear as multiple small varices containing pools of blood lying within them or at their edges.[15]

Microscopically the appearance of the spleen in the initial stage of sickle cell anemia is similar to its appearance in cases of hemolytic jaundice except for the characteristic shape of the red cells. In the later stages there are certain fundamental differences: 1. The characteristic transformation of the enlarged spleen into a fibrotic, extremely atrophied organ does not occur with hemolytic jaundice as with sickle cell anemia. 2. Except in the spleen, no engorgement of other organs with red cells is noted in cases of hemolytic jaundice. In the presence of hemolytic jaundice the lungs, lymph nodes, kidneys and liver are normal except for some hyperactivity of the Kupffer cells in certain exceptional cases.[16]

The tremendous engorgement of the reticulum meshes has been variously explained. Diggs [15a] considered it to be due at least partially to hemorrhages around the terminal arterioles, though, as Ryerson and Terplan [9] noted, it is extremely difficult to distinguish areas of actual hemorrhage from pools of blood in the distended reticulum meshes. Rich [17] stated the belief that congenital malformations of the sinusoids account for a free escape of blood into the red pulp (which perhaps further supports the concept of "status degenerativus"), but Ryerson and Terplan [9] pointed out that the passage of blood from the sinusoids into the reticulum meshes may be a physiologic process rather than the result of a congenital defect.

Engorgement with disfigured red blood corpuscles similar to that observed in the spleen is also encountered in the distended capillaries of the liver, lymph nodes, lungs, kidneys and other organs in cases of sickle cell anemia. In a personally observed case the blood vessels of the cortical portions of both kidneys were filled with sickle cells so closely packed together as to resemble coagulum, though no fibrin could be found in the masses.

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15. (*a*) Diggs, L. W.: Siderofibrosis of the Spleen in Sickle Cell Anemia, J. A. M. A. **104**:538 (Feb. 16) 1935. (*b*) Jaffé, R. H.: The Reticulo-Endothelial System, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 2, p. 973. (*c*) Ryerson and Terplan.[9]

16. Meulengracht, E.: Chronic Hereditary Hemolytic Jaundice, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 3, p. 2281.

17. Rich, A. R.: The Splenic Lesion in Sickle Cell Anemia, Bull. Johns Hopkins Hosp. **43**:398, 1928.

Another rather constant observation in cases of sickle cell anemia is proliferation of the hepatic Kupffer cells and of the reticuloendothelial cells of the lymph nodes.

There can be little doubt that the abnormal configuration of the erythrocytes must be the cause of the engorgement which they produce in the small arterioles and capillaries.[18] The elongated, distorted red corpuscles cannot pass through the narrow vessels as readily as normal cells, and more or less marked stasis follows the attempted passage of great numbers of characteristically deformed cells. The engorgement is particularly frequent in those organs in which the rate of blood flow is unusually slow and the oxygen tension, as a result, is unusually low. It is for these reasons that the particular, though by no means the exclusive, sites of stagnation are the spleen, the liver and the lymph nodes. This concept, which has been supported by Diggs [15a] and Yater and Hansmann,[18a] is in my opinion the only satisfactory explanation of the microscopic observations associated with sickle cell anemia.

The essential pathologic process in sickle cell anemia, then, is the stagnation and conglutination of disfigured red corpuscles which has just been described. The serious consequences which follow can readily be deduced from one's knowledge of general pathology, that is, one's knowledge of the typical biologic reaction of the organism to long-standing circulatory stagnation. They include: (1) thrombosis; (2) ischemia, necrosis and fibrosis, and (3) resolution of the red blood cells with subsequent anemia.

1. *Thrombosis.*—Slowing of the blood stream predisposes to thrombosis, followed by endarteritis and infarction, which is a frequent observation in cases of sickle cell anemia. The arterioles of the spleen, the lungs and the brain are particularly likely to be affected. A somewhat different explanation, however, must be advanced for the obliterating endarteritis of the medium and large cerebral vessels described by Bridgers [19] in the case of a child affected with sickle cell anemia, as well as for the arteriolosclerosis observed by Yater and Hansmann [18a] in the pulmonary arteries. At present it is impossible to determine whether previous thromboses and the frequent biologic inferiority of the vascular system in the Negro race are to be considered as causative factors.

2. *Ischemia, Necrosis and Fibrosis.*—Whether or not the circulatory stagnation caused by the deformed sickle cells results in actual thrombosis, the conglutination of the packed cells necessarily produces the same effects in the affected tissues. Ischemia, necrosis, endarteritis, fibrosis,

18. (*a*) Yater, W. M., and Hansmann, G. H.: Sickle Cell Anemia: A New Cause of Cor Pulmonale, Am. J. M. Sc. **191**:474, 1936. (*b*) Diggs.[15a]

19. Bridgers, W. H.: Cerebral Vascular Disease Accompanying Sickle Cell Anemia, Am. J. Path. **15**:353, 1939.

hyalinization and deposition of blood pigment and calcium are characteristic of the transformation of the initially enlarged spleen into the atrophic, sclerotic organ observed later (Diggs [15a]). Analogous changes may take place in other organs. In a case personally observed and previously referred to, the small blood vessels of the renal cortex were engorged with sickle cells, and massive bilateral cortical necrosis was a striking and unusual postmortem observation. The clinical implications of this case are also worthy of mention. The patient, a 10 year old Negress, was operated on for a thyroglossal cyst without recognition of her sickle cell disease. After operation she showed signs of renal disease, and an antemortem diagnosis of acute nephritis was made. Just before death the nonprotein nitrogen content of the blood was 120 mg. per hundred cubic centimeters. Actually the child died from an atypical sequela of her sickle cell trait. It was not the anemia but the sickling of the red corpuscles which was responsible for the fatal outcome.

3. *Resolution of Red Corpuscles and Anemia.*—Stagnation and conglutination of red corpuscles, such as are seen in cases of sickle cell anemia, must eventually lead to disintegration of the corpuscles, again without regard to whether or not thrombosis develops. There would seem to be no other pathologic state in which an engorgement of the small blood vessels of various organs, with subsequent stasis and impaction of erythrocytes, occurs to such a degree and for such long periods as in sickle cell anemia. The disintegration of the conglutinated red cells sets free hemoglobin, which is transformed into the blood pigment found in various organs and into the bilirubin found in increased amounts in the blood serum. The dead corpuscles and shadows finally disappear as the result of the phagocytic action of the reticuloendothelial cells, which are seen in full activity and proliferation in the spleen, liver, bone marrow and lymph nodes. The microscopic picture of the small, firm, fibrotic spleen associated with sickle cell anemia has been described by Diggs.[15a]

> The pulp, instead of being a mass of erythrocytes as in the early stages, is now a mass of reticulum between which the packed sickled cells lie in capillary-like spaces. In some spleens the sinusoids are greatly dilated and tortuous and their endothelial cells are hypertrophied. Pigment granules are conspicuous in the organizing lobules and there is phagocytosis of erythrocytes by macrophages. Giant cells and branching filaments are occasionally seen.

I have myself seen this microscopic picture and have also observed the proliferation of Kupffer cells in the liver and of the reticuloendothelial cells in the lymph glands "stuffed with disfigured erythrocytes," as described by Jaffé.[15b]

If the concept of the pathogenesis of the anemia of sicklemia which I have just set forth is accepted, it is clear that anemia is merely one of the disastrous consequences of the sickle cell trait and, as a rule, not its most

dangerous consequence. The hemolytic anemia is merely the most obvious and most readily recognizable clinical sign of the ailment, which would more reasonably be termed sickle cell disease than sickle cell anemia.

Anemia, furthermore, is not one of the very early consequences of the disease. It develops only when the regenerative power of the bone marrow no longer has the ability to compensate for the increased number of red blood cells destroyed. As long as compensation exists, no anemia can be demonstrated, which is also the case with hemolytic jaundice and Cooley's disease. Microscopic signs of precipitated regeneration are found in both the circulating blood and the bone marrow in cases of sickle cell anemia. Direct involvement of the bone marrow by the fundamental process of sickle cell disease (that is, circulatory stagnation and its consequences) brings about a progressive impairment of the regenerative power of the bone marrow and enhances the development of anemia.

CLINICAL SIGNS AND SYMPTOMS

The clinical symptoms and signs of sickle cell disease are not difficult to explain in the light of the concept that the disease is due to conglutination of the deformed erythrocytes and to the consequences of this process. Certain of these clinical manifestations, while they are by no means specific, are of great value in arousing the suspicion that sickle cell disease may be present.

1. Slowly healing, nonvaricose superficial ulcers of the leg, which may be present even in childhood, are clinically important, even though neither the clinical appearance nor the microscopic structure shows specific features. The slow circulation in the lower limbs facilitates their development, but it is no more known whether or not thrombosis plays a role in their production (Diggs) than it is known whether temporary arteriolar and capillary engorgement with sickled cells is responsible. Similar ulcers have been observed in persons with constitutional hemolytic jaundice.[20]

2. Changes in the bones are less frequent than are ulcers of the leg, though the same rarefication of the cancellous bones and the same "moth-eaten" and "hair on end" appearance of the skull are observed with sickle cell disease as with Cooley's erythroblastic anemia and, to a milder degree, with hemolytic jaundice,[21] and it is quite possible that

20. Taylor, E. S.: Chronic Ulcer of the Leg Associated with Congenital Hemolytic Jaundice, J. A. M. A. **112**:1574 (April 22) 1939. Leger, L. H., and Orr, T. G.: Chronic Leg Ulcerations in Congenital Hemolytic Jaundice, South. M. J. **33**:463, 1940.

21. (*a*) Gaensslen, M.: Skelettveränderungen bei Blutkrankheiten, in Libro de Oro dedicado al Dr. Mariano R. Castex, Buenos Aires, 1938, vol. 2, p. 507. (*b*) Meulengracht.[16]

they may contribute, at least partially, to the "rheumatic" pains of which these patients complain. Such migrating pains in the bones, joints and muscles are far more frequent than are demonstrable osseous changes, and it seems entirely justifiable to classify them among the specific manifestations of the disease. This type of "rheumatoid pain" in cases of sickle cell disease would be somewhat related causatively to the hypertensive type of so-called "rheumatism" described many years ago.[22]

3. Rheumatoid and abdominal pains, which occasionally become excruciating (so-called abdominal crises) are characteristic. Thrombotic processes are believed to account for these manifestations. Vascular engorgement, however, with subsequent stagnation of the blood stream, may have a similar effect.

4. Cardiac symptoms and signs in patients with sickle cell anemia frequently simulate the effect of a mitral valvular lesion of rheumatic origin. Differential diagnosis is difficult if not impossible, as I have observed in several cases. The diagnosis is particularly difficult with patients who run a low grade fever and who complain of "rheumatic pains." Sickling, hemolytic anemia and a sedimentation rate within normal limits do not necessarily rule out a concomitant active or old rheumatic lesion of the heart, but in the majority of such cases a diagnosis of rheumatic valvular disease will probably be wrong.[23] Yater and Hansmann [18a] satisfactorily explained the cardiac signs associated with sickle cell disease by describing a noninflammatory "thromboangiitis obliterans," capillary stasis and thrombosis in the lungs in 2 cases in which the diagnosis of mitral stenosis, made ante mortem, proved incorrect at autopsy.

5. The liver may be affected. Ryerson and Terplan,[9] for instance, have described a case of sickle cell disease in which subacute yellow atrophy of the liver was diagnosed clinically and demonstrated at autopsy. Such a "complication," to my mind, is not merely accidental. In microscopic preparations in cases of sickle cell disease I have observed not only distention of the hepatic sinusoids by packed sickle cells but definite signs of damage to the liver cells themselves. They may be somewhat compressed and in some areas may show vacuolization, fatty change and necrosis. Some cells may lose contact with the liver cell cords and lie separated and surrounded by proliferated Kupffer cells and perivascular accumulations of lymphocytes and mononuclear cells. Some degree of periportal fibrosis is frequently seen. It is not inconceivable that such an exceptionally extensive alteration of the liver cells may provide the

22. Bauer, J.: Hochdruckrheumatismus, Verhandl. d. 33 Kong. d. deutsch. Gesellsch. f. inn. Med., 1922, p. 436; Der sogenannte Rheumatismus, Dresden, Theodor Steinkopff, 1929.

23. King and Janeway,[7] Haden and Evans.[11]

substratum for what is usually termed hepatitis (catarrhal jaundice) and might better be called hepatosis and that such a condition might eventually lead to acute or subacute hepatic atrophy.

This type of hepatosis, usually of rather mild degree and course, probably occurs in association with sickle cell disease more frequently than is usually realized. Dale [24] reported a case of this association. A 14 year old Negress first gave a positive indirect van den Bergh reaction and later a biphasic reaction in the serum; the stool did not contain bile or the urine urobilin. A few days later both reactions became positive. The same author mentioned the occasional occurrence of a positive direct van den Bergh reaction in the serum of patients with sickle cell anemia, although as a rule this reaction is positive only in the indirect phase.

Another illustrative case,[25] still under observation at Charity Hospital of Louisiana at New Orleans, may be cited.

A Negress, first seen at the age of 19 years in April 1937, at that time was in a severe active phase of sickle cell disease. The red cell count was 752,000 and the white cell count 12,300 per cubic millimeter. An ulcer had been present on the right ankle for four months and healed only when the patient reached the latent phase, in September 1937. At that time there were 4,420,000 erythrocytes per cubic millimeter and 90 per cent hemoglobin (Sahli). During 1939 and 1940 repeated examinations showed the red cell count to be more or less constantly 2,500,000 per cubic millimeter and the hemoglobin 50 per cent. The icterus index during this period was 20, the value for serum bilirubin 4.8 mg. per hundred cubic centimeters, and the van den Bergh reaction indirect positive.

The patient has had two definite attacks of hepatosis (catarrhal jaundice), diagnosed by a marked increase in jaundice, temporary enlargement of the liver, a temporary positive direct van den Bergh reaction in the blood serum and a positive hippuric acid reaction indicative of functional disturbance of the liver cells.

6. Other clinical manifestations are less frequent. Cerebral manifestations, usually diagnosed as thrombosis or intracranial hemorrhage, have frequently been reported within recent years.[26] The fundamental anatomic lesion seems to be the engorgement of greatly congested capillaries with sickled erythrocytes. Some type of thromboangiitis obliterans, with multiple areas of perivascular hemorrhages and focal necrosis, could reasonably be considered a consequence of hemostasis and engorgement. Large subarachnoid hemorrhages and thrombosis of the dural sinus have

24. Dale, G. C.: Sickle Cell Anemia, South. Med. & Surg. **49**:14, 1937.

25. This case will be reported in detail by Dr. R. C. Lowe.

26. Arena, J. M.: Cerebral Vascular Lesions Accompanying Sickle Cell Anemia, J. Pediat. **14**:745, 1939. Yater and Hansmann.[18a] Bridgers.[19]

also been observed. Massive necrosis of the renal cortex has previously been mentioned as the result of impaction of sickled cells in the small vessels of the kidneys.

RELATION OF SICKLING AND SICKLE CELL DISEASE

Whether sicklemia invariably precedes the development of sickle cell anemia is still a matter of debate. Mason [1] stated that proof of the thesis is lacking and also expressed doubt whether sicklemia persists through the life of the affected person. For my own part, on the basis of clinical and biologic evidence, I believe that sicklemia is a necessary predisposing factor in the development of sickle cell anemia.

This point of view is in complete accordance with the established facts concerning other constitutional abnormalities of the red blood corpuscles. The spherocytosis and microcytosis characteristic of constitutional hemolytic jaundice, for instance, may be present without jaundice and without anemia in so-called compensated cases in families of persons suffering from this disease (Gaensslen,[27] Bauer [8] and others). An analogous "compensated" state has been described in connection with Cooley's disease without anemia (Wintrobe and others [28]), and in 1 case overcompensation seemed to exist. The patient had 6,440,000 red corpuscles per cubic millimeter of blood, and there were microcytosis, hypochromia, marked stippling of the red cells, "target cells," increased resistance of the erythrocytes to hypotonic saline solutions and splenomegaly. Similar observations have been made in cases of ovalocytosis, which usually represents a harmless abnormal constitutional variation in the shape of the red cells but which may lead to anemia in some persons.[29]

When and under what circumstances the sickle cell trait is converted into sickle cell disease is still not entirely clear. The sickle cell trait is found in about 7.5 per cent of North American Negroes, but these Negroes are chiefly of mixed blood, and no information is available as to the frequency with which it is found in pure bred Negroes in Africa. Only a certain proportion of persons who exhibit the trait, however, actually suffer from sickle cell anemia. Sydenstricker set the proportion at 1.5 per cent.[1] Dale [24] and Johnson and Townsend [30] reported a per-

27. Gaensslen, M.: Ueber haemolytischen Icterus, Deutsches Arch. f. klin. Med. **140**:210, 1922.

28. Wintrobe, M. M.; Matthews, E.; Pollack, R., and Dobyus, B. M.: A Familial Hemopoietic Disorder in Italian Adolescents and Adults, J. A. M. A. **114**:1530 (April 20) 1940.

29. Mason, V. R.: Ovalocytosis, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 3, p. 2349. Gaensslen.[21a]

30. Johnson, F. B., and Townsend, E. W.: Sickle Cell Anemia, South. Med. & Surg. **49**:377, 1937.

centage as high as 10. Huck,[6] by systematic blood tests, showed that in Negroes with sicklemia but without clinical signs or symptoms of sickle cell anemia, sickling was observed in 25 per cent of the red cells. In persons with mild signs of the disease the proportion rose to 75 per cent.

The discrepancy in the estimates is apparently due to the highly variable course of the disease. Some persons die from it in early childhood; some live for decades in spite of recurrent acute attacks, and some never present any clinical evidence of the disease, which is demonstrated only by the characteristic observations at necropsy. Diggs,[15a] in this same connection, emphasized, I think correctly, that either a large and congested or a small and atrophic spleen may be found in children as well as in adults, "which indicates that the active disease may occur in varying age periods or that the rate of progression of the lesion is highly variable."

The first clinical manifestations of the disease may be preceded by some acute infectious disease or may be precipitated, as has already been pointed out, by some surgical procedure. Under these circumstances thrombosis is facilitated, and any factors which cause slowing of the circulation may also play a part in converting sicklemia into sickle cell disease, provided a sufficient number of erythrocytes are affected with the pathologic trait.

From what has been said certain statements seem to be justified:

1. The sickle cell trait shows individual differences in intensity, that is, in the number of affected cells.

2. The mechanism which converts sicklemia into sickle cell disease may be set into action if a sufficiently large number of cells are affected and if conditions particularly favorable for sickling are present.

3. Such conditions include local or general anoxemia, infectious diseases, surgical procedures and other circumstances and factors which are known to slow the circulation of the blood.

4. In view of these differences, it is easy to understand why sickle cell disease varies so widely as to age of onset, clinical picture and course.

Sicklemia, as has been pointed out, must be distinguished from true sickle cell disease. In the same manner, active and latent sickle cell disease with and without anemia must be distinguished from each other. The latent phase of the disease may be described as a condition of subjective health which represents a period of apparent recovery following a period of ill health due to the disease. At this time the only demonstrable signs are sickling of the red cells, anemia, which is usually mild, and bilirubinemia. A picture of this kind indicates that the patient is not merely predisposed to sickle cell disease but is actually affected with it.

It must be remembered, in the same connection, that sickling is a reversible phenomenon. That is why the observations at autopsy are

not constant. It is possible to find only the residua of the circulatory stagnation formerly present in the various organs. Not always does one find the engorgement with packed sickled cells where endarteritis, fibrosis and proliferation of reticuloendothelial cells indicate the presence of sickle cell disease. To put it another way, although autopsy often reveals merely a special stage of the disease, it practically always permits also conclusions as to its past course.

REPORT OF SPECIAL CASES

It occasionally happens that a cellular reaction produced by a pathologic process far surpasses the original aim of this reaction,[31] as the following case illustrates.

CASE 1.—I. T., a 33 year old Negro, had complained for three years of numbness in the legs, pains in the lower extremities and elsewhere, dyspepsia with occasional vomiting, abdominal pain, headache, vertigo, dyspnea on slight exertion, weakness and fatigue. He had had several epileptiform seizures and occasionally had low grade elevations of temperature. His chief complaint when he was first seen was of obstinate ulcers of the leg.

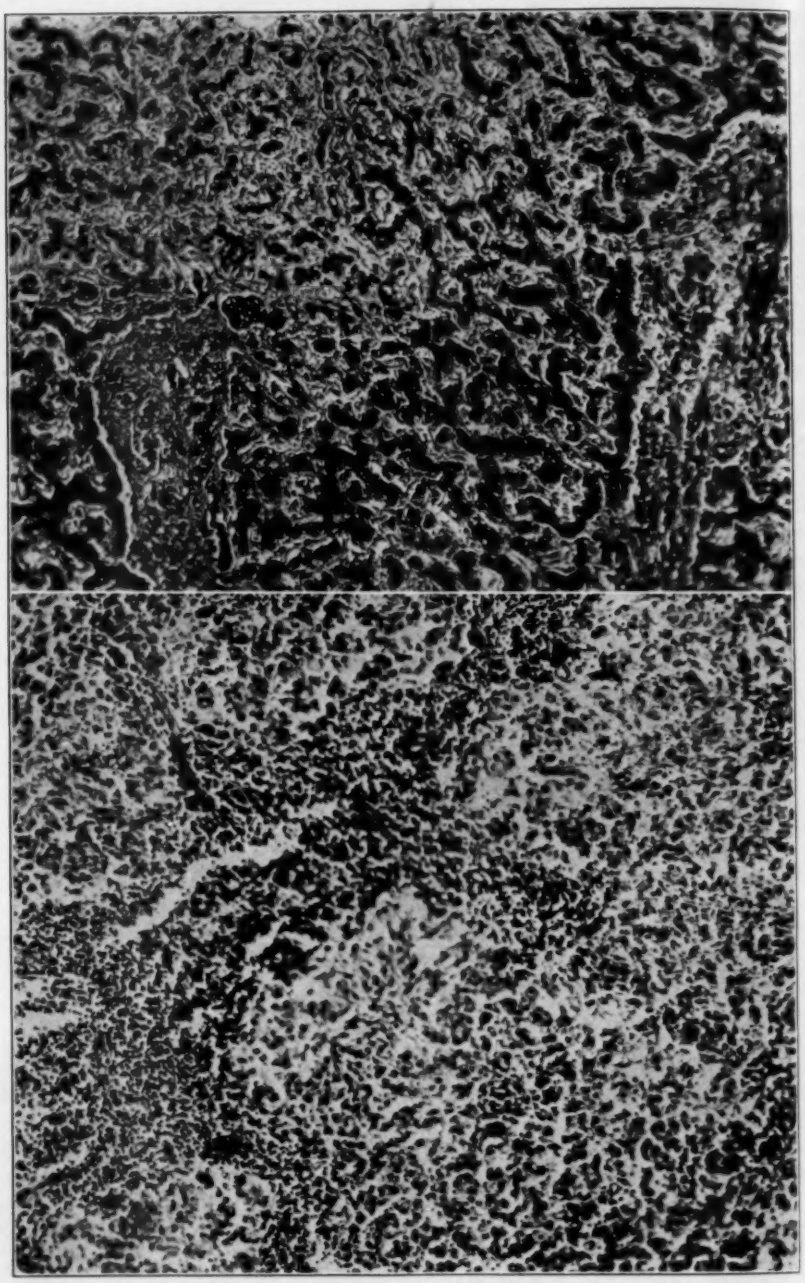
Physical examination revealed him to be anemic and subicteric, with a markedly enlarged heart and a blowing systolic murmur over the apex. Roentgen examination revealed considerable enlargement of the transverse cardiac diameter and unusual porosity of the skull, particularly in the frontal region. The electrocardiogram revealed no abnormalities. The blood pressure was 130 systolic and 80 diastolic.

Serologic tests for syphilis gave negative results, and examination of the cerebrospinal fluid revealed no abnormalities. The red cell count was 2,735,000 and the white cell count 13,000 per cubic millimeter of blood. The value for hemoglobin was 50 per cent (8 Gm.). Polychromatophilia, anisocytosis and poikilocytosis were observed, and 80 to 90 per cent of the red cells showed definite sickling at the end of twelve hours in a wet preparation at 37 C. Numerous nucleated erythrocytes were present. On subsequent examinations the red cell count reached a minimum of 1,900,000 per cubic millimeter. The indirect van den Bergh reaction was positive, and the value for serum bilirubin 5.5 mg. per hundred cubic centimeters.

The patient was given a transfusion when examination of the blood showed 2,300,000 red cells per cubic millimeter, 7.7 Gm. of hemoglobin and a hematocrit value of 17.5 per cent. The temperature was 102 F. and the blood pressure 122 systolic and 90 diastolic. When the patient had been given 200 cc. of cross-matched compatible blood by the direct method he complained of abdominal pain and dyspnea. The transfusion was stopped at once but death occurred unexpectedly five hours later.

Postmortem Examination.—The spleen, which weighed 15 Gm., was highly atrophic, whitish and composed of fibrous trabeculae, with no remaining pulp. The liver, which weighed 3,200 Gm., was slate brown and markedly enlarged. On section the normal architecture was obliterated. The gallbladder was enlarged

31. Bauer, J.: Adaptation and Compensation as Origin of Disorders, Ann. Int. Med. **1**:875, 1928.



The lower photomicrograph, of a lymph node, shows nodular proliferation of reticulum cells in a case of sickle cell disease with reticuloendotheliosis. The upper photomicrograph, of a section of the liver, shows engorgement of the sinusoids with sickle cells, marked proliferation of Kupffer cells and degenerative and necrotic changes in some of the liver cells in a case of sickle cell disease with reticuloendotheliosis.

and contained a number of stones; the wall was thickened. The heart, which weighed 370 Gm., was moderately enlarged. The right ventricular muscle was nearly 0.5 cm. and the left 1 cm. in thickness. The lungs were greatly congested, and large amounts of red, frothy fluid exuded from the cut surfaces.

The most striking observation was the tremendous enlargement of the mediastinal, tracheobronchial and abdominal lymph nodes, especially along the aorta and the gastrohepatic region. The largest measured 4 cm. in diameter. The color varied from anthracotic in the tracheobronchial region to grayish brown and whitish. No caseation was observed, and no signs of tuberculous infection were seen anywhere in the body.

Microscopic preparations of the lymph nodes showed a marked increase in the reticular tissue, which was responsible for their enlargement. Numerous nodules, which were well defined and composed of proliferating reticular cells, formed the chief components of the lymphatic glands. They were of varying sizes and consisted of large, light cells rich in acidophilic protoplasm and interlacing with each other by fine protoplasmic processes and filaments. The small blood vessels were engorged with sickled cells, and blood pigment was deposited around some of the vessels. Sickled cells were also found in the meshes of the reticulum, and phagocytosis could be seen in various areas. In some lymph glands hyalinization and sclerosis replaced the reticulum nodules.

The small vessels of the liver were engorged with sickled cells. There was marked proliferation of Kupffer's cells, and phagocytosis and signs of alteration of the liver cells were observed in some areas. Some liver cells were detached from the liver cell cords and showed vacuolation and atrophy. Large amounts of blood pigment were present.

The other organs showed the characteristic microscopic picture of sickle cell anemia.

Comment.—The first impression after postmortem examination in this case was that the condition was atypical tuberculosis. It was somewhat supported by the observation of occasional giant cells among the proliferating reticuloendothelial cells but was disproved by the absence of tubercles and the negative results of guinea pig inoculation. The obvious diagnosis, therefore, was reticuloendotheliosis of a prevalently reticular type. I agree with Jaffé [15b] that this condition is not characteristic of any particular infection but merely indicates abnormal irritability of the reticuloendothelial system, either acquired or congenital. The hyperplasia of the involved cells may be either nodular or diffuse.

The picture in this case was merely the characteristic one of sickle cell anemia exaggerated to an extreme degree. Jaffé [15b] mentioned that the Kupffer cells in the liver and the reticuloendothelial cells of the para-aortic and abdominal lymph nodes are engorged with disfigured erythrocytes in cases of sickle cell anemia, and my own observations confirm this statement. A more or less generalized enlargement of the lymph nodes has also been observed by Mason,[1] Dale [24] and Johnson and Townsend.[30] Enlarged mesenteric lymph nodes may frequently be observed at operation or at autopsy, and it therefore seems justifiable to consider the

reticuloendotheliosis present in this case as an unusual consequence of the sickle cell disease and as representative of a special variety of this rare syndrome of varied causation.

It should be noted that giant cells of the foreign body variety have been described by Diggs [15a] as present in the spleen in sickle cell anemia and are common in cases of reticuloendotheliosis, as in this case.

A case of typical polycythaemia vera combined with the sickle cell trait [25] may also be cited.

CASE 2.—A 45 year old Negress showed a characteristic dusky red appearance of the mucous membranes. The spleen was slightly enlarged. Examination of the blood showed 8,250,000 red cells and 6,500 white cells per cubic millimeter. The value for hemoglobin was 145 per cent (21 Gm.), and the hematocrit value was 75. The blood volume was markedly increased, and 50 per cent of the red corpuscles were found to be sickling in the sealed preparation.

Comment.—It should be emphasized that this particular case represents true erythremia, as contrasted with the slight erythrocytosis observed by Wintrobe and his associates [28] in certain cases of "compensated" Cooley's disease.

It is interesting to observe that the constitutional sickle cell trait can be associated with polycythemia. I hesitate, however, to postulate that polycythemia might be induced by an exaggerated regenerative reaction of the bone marrow due to sickle cell disease, particularly since no indication of previous excessive destruction of red cells was found. This case also shows that sicklemia need not produce deleterious consequences even in the presence of polycythemia, which might be expected to increase the predisposition to thrombosis.

THERAPEUTIC CONSIDERATIONS

The concept of the pathologic physiology of sickle cell disease advanced in this paper clearly requires institution of certain preventive measures and maintenance of a certain therapeutic point of view. If these precautions are disregarded, the consequences of the sickle cell trait may be of important and even fatal significance.

It is clear that splenectomy is of no practical value in the management of the disease. This opinion is commonly accepted by all authorities today. As Diggs [15a] expressed it, if the patients are left alone, they will "in effect splenectomize themselves without the benefit of surgery." Iron therapy rather than liver extracts would seem to be indicated for combating the anemia, and blood transfusions are commonly used.

The anemia, however, is not the most important consideration. The circulatory stasis due to engorgement of the small blood vessels by the disfigured red cells is the primary cause not only of the anemia but of

the clinical symptoms of the disease. Furthermore, it is its most serious manifestation. It is the factor responsible for the surgical risk and for what may be termed the biologic risk with such persons.

It seems logical, therefore, that all available measures to counteract circulatory stasis should be applied. Sufficient muscular exercise, massage and avoidance of unnecessarily prolonged rest in bed in accidental illnesses are of prophylactic value. Cool baths or douches may be useful in dilating the blood vessels of the internal organs by constriction of the peripheral vessels, and hot enemas may bring about dilatation of the abdominal blood vessels. Saline and dextrose infusions and blood transfusions may help to prevent circulatory stagnation. Fluids should be forced. Thyroid medication, which is a valuable method of increasing the circulatory velocity, should be part of the preparation for operation under certain circumstances. Oxygen inhalations may be beneficial in counteracting local anoxemia and therefore in inhibiting sickling of the red cells. Such measures are all theoretically sound, but their practical value can be determined only by extensive experience with them.

One prophylactic measure, however, can and should be applied routinely. All Negro patients in both medical and surgical services should be tested routinely for sicklemia. By this method sickle cell disease could be differentiated from such pathologic conditions (with which it is frequently confused) as rheumatic fever, rheumatic heart disease, polyarthritis, osteomyelitis, typhoid fever and other infectious diseases, cerebral disease, peptic ulcer, appendicitis and cholecystitis.[2a] It is particularly important that patients in surgical services should be so tested and that a positive result be regarded as calling for a revision of the indications for the proposed operation. Surgical treatment should not be given until the measures outlined have been instituted and carried out.

My own feeling is that routine testing of the blood of Negro patients for sickling would save some lives which are now being lost because this simple precaution is omitted. In that respect it is perhaps more valuable than many other laboratory tests which are far more complicated and time consuming and which are being used indiscriminately and without special indications.

SUMMARY

The sickle cell trait (sicklemia) is an inborn and constitutional abnormality of the erythrocytes which is encountered almost exclusively in the Negro race.

Only a few of the persons affected with this trait have sickle cell anemia. Persons suffering from sickle cell anemia are often placed in jeopardy if they have various intercurrent diseases. Surgical procedures also introduce a serious element of risk.

Unexpected deaths after operation are sometimes demonstrated at necropsy to have been caused by sickle cell anemia, which frequently was not diagnosed because it was not suspected and therefore was not searched for.

Anemia is only one consequence of the sickle cell trait and, as a rule, is not its most dangerous consequence. Circulatory stasis in the small blood vessels of the internal organs is the primary and the most disastrous consequence of sicklemia. Such stasis may be enhanced by surgical procedures. Sickle cell disease would therefore be a more logical term for this condition than sickle cell anemia.

The anemia associated with the disease, as well as other symptoms and signs, can be explained as a consequence of circulatory stasis due to mechanical obstruction of the blood vessels by the disfigured, elongated erythrocytes.

Parenchymal lesions of the liver may occur in association with sickle cell disease.

Cases of sickle cell disease presenting unusual clinical and pathologic pictures are reported, including a case of massive bilateral cortical necrosis of the kidney, a case of reticuloendotheliosis and a case of polycythaemia vera in which the sickle cell trait was apparent.

The concept of sickle cell disease presented leads logically to special prophylactic and therapeutic considerations.

RESPONSE OF PLASMA PROTHROMBIN TO VITAMIN K SUBSTITUTE THERAPY IN CASES OF HEPATIC DISEASE

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Considerable experimental and clinical data now at hand implicate the liver as the site of prothrombin formation.[1] Prothrombin deficiency has been reported as occurring in human subjects suffering from damage to the liver even though no biliary obstruction or fistula was present.[2] Wilson[3] reported that in disease of the liver the degree of hypoprothrombinemia was directly proportional to the amount of hepatic damage as indicated by the hippuric acid test.

The data presented here are concerned with prothrombin studies made on 12 patients with various types of disease of the liver and a lowered level of plasma prothrombin. The initial value for prothrombin, the values after three days, one week and two weeks of treatment and the diagnosis in each case are presented in the table. The prothrombin determinations were made by a modified one stage procedure described elsewhere.[4] Each patient received 8 mg. of 2-methyl-1, 4-naphthoquinone daily by mouth, accompanied with bile salts.

In the cases reported here there was either a complete failure of response to the naphthoquinone (cases 1 to 10) or a delayed rise of

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1. Warner, E. D.: Plasma Prothrombin: Effect of Partial Hepatectomy, J. Exper. Med. **68**:831 (Dec.) 1938. Warren, R., and Rhoads, J. E.: The Hepatic Origin of the Plasma Prothrombin, Am. J. M. Sc. **198**:193 (Aug.) 1939. Pohle, F. J., and Stewart, J. K.: Observations on the Plasma Prothrombin and the Effects of Vitamin K in Patients with Liver or Biliary Tract Disease, J. Clin. Investigation **19**:365 (March) 1940.

2. Kark, R., and Lozner, E. L.: Nutritional Deficiency of Vitamin K in Man, Lancet **2**:1162 (Dec. 2) 1939.

3. Wilson, S. J.: Quantitative Prothrombin and Hypuric Acid Determinations as Sensitive Reflectors of Liver Damage in Humans, Proc. Soc. Exper. Biol. & Med. **41**:559-561 (June) 1939.

4. Allen, J. G.; Julian, O. C., and Dragstedt, L. R.: Use of Serial Dilutions in Determination of Prothrombin by the One Stage Technic, Arch. Surg. **41**:873 (Oct.) 1941.

prothrombin (cases 11 and 12). This is strikingly different from the reaction seen in patients with hypoprothrombinemia due to obstructive jaundice, in whom the prothrombin response to similar doses of naphthoquinone and bile salts was very rapid. Without exception the value reached normal within twenty-four to thirty-six hours after initiation of

Prothrombin Response to 2-Methyl-1, 4-Naphthoquinone in Cases of Disease of the Liver

Case Number	Diagnosis	Prothrombin, Per Cent: Initial	3 days After Treatment	1 Week After Treatment	2 Weeks After Treatment	Daily Dose of Naphthoquinone, Mg.	Comment
1	Alcoholic cirrhosis	48	48	48	48	8	Icterus
2	Alcoholic cirrhosis	23	25	29	..	8	Marked icterus; died on 7th day; diagnosis confirmed at autopsy
3	Alcoholic cirrhosis	22	22	20	..	8	Marked icterus; died on 8th day
4	Alcoholic cirrhosis	35	33	30	26	8	Slight icterus; died on 15th day
5	Cardiac cirrhosis	43	37	53	55	8	Marked icterus; died on 23d day
6	Wilson's disease	78	64	61	63	8	No icterus
7	Fatty infiltration with peritonitis	46	43	48	40	8	Slight icterus; died on 33d day
8	Multiple abscesses of liver	57	56	54	..	8	Marked icterus; died on 7th day
9	Acute yellow atrophy	10	15	..	..	8	Marked icterus; hemorrhagic diathesis; died on 4th day
10	Acute yellow atrophy	48	34	50	..	8	Marked icterus; died on 7th day
11	Acute hepatitis	41	68	95	..	8	Marked icterus
12	Metastatic carcinoma	57	62	100	100	8	No icterus

therapy, even though in some instances the obstruction had been present unremittingly for several months.[5]

It will be seen that patients with chronic disease of the liver showed the most marked failure to respond to therapy. This, we believe, offers a characteristic of valuable diagnostic importance, in that failure of

5. Allen, J. G., and Julian, O. C.: Clinical Use of a Synthetic Substance Resembling Vitamin K (2-Methyl-1, 4-Naphthoquinone), Arch. Surg. **40**:912 (May) 1940.

prothrombin response to adequate vitamin K therapy in cases of jaundice would imply intrahepatic disease rather than obstruction of the bile ducts as the cause of the jaundice.

SUMMARY

The rate and amount of rise in plasma prothrombin in 12 patients with proved disease of the liver given adequate vitamin K (2-methyl-1, 4-naphthoquinone) therapy are reported. The prothrombin response in these patients is contrasted with that seen in cases of hypoprothrombinemia due to bile duct obstruction or fistula, previously reported. It is suggested that the striking difference noted is of diagnostic significance.

TIME REQUIRED FOR BLOOD TO FLOW FROM THE ARM AND FROM THE FOOT OF MAN TO THE CAROTID SINUSES

I. EFFECT OF TEMPERATURE, EXERCISE, INCREASED INTRAMUSCULAR TENSION, ELEVATION OF LIMBS AND SYMPATHECTOMY

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No attempt has been made to review the literature on circulation time completely for this presentation. Extensive references may be found elsewhere.[1] All methods depend on determination of the time elapsing between intravascular injection of a substance and its arrival at another part of the body. This arrival may be determined objectively [2]

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Abridgment of part of a thesis submitted by Dr. Smith to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Medicine.

1. (*a*) Smith, L. A.: The Postoperative Arm-to-Carotid Sinus and Foot-to-Carotid Sinus Circulation Time in Man, with Special Reference to Effect of the Administration of Extract of Thyroid Gland, Thesis, University of Minnesota Graduate School, 1939. (*b*) Kvale, W. F., and Allen, E. V.: The Rate of the Circulation in the Arteries and Veins of Man: I. Studies of Normal Subjects and of Those with Occlusive Arterial Disease and Hyperthyroidism, Am. Heart J. **18**:519, 1939. (*c*) Kvale, W. F.; Allen, E. V., and Adson, A. W.: The Rate of the Circulation in the Arteries and Veins of Man: II. Studies of Hypertension, of Orthostatic Hypotension and of the Effects of Sympathectomy, ibid. **18**: 537, 1939. (*d*) Kvale, W. F., and Allen, E. V.: The Rate of the Circulation in the Arteries and Veins of Man: III. The Influence of Temperature of the Skin, Digestion, Posture, and Exercise, ibid. **18**:546, 1939; (*e*) An Error in the Sodium Cyanide Method of Determining Speed of Venous Blood Flow, ibid. **18**:557, 1939.

2. (*a*) Koch, E., cited by Tarr, Oppenheimer, and Sager.[3] (*b*) Blumgart, H. L., and Yens, O. C.: Studies on the Velocity of Blood Flow: I. The Method Utilized, J. Clin. Investigation **4**: 1, 1927. (*c*) Thompson, W. O.; Alper, J. M., and Thompson, P. K.: The Effect of Posture upon the Velocity of Blood Flow in Man, ibid. **5**:605, 1928. (*d*) Hamilton, W. F.; Moore, J. W.; Kinsman, J. M., and Spurling, R. G.: Simultaneous Determination of the Pulmonary and Systemic

(Footnote continued on next page)

or subjectively.[3] Loevenhart and his associates [4] noted marked respiratory stimulation in animals and man following intravenous injection of a solution of sodium cyanide and proposed the use of sodium cyanide

Circulation Times in Man and of a Figure Related to the Cardiac Output, Am. J. Physiol. **84**:338, 1928. (*e*) Kinsman, J. M.; Moore, J. W., and Hamilton, W. F.: Studies on the Circulation: I. Injection Method; Physical and Mathematical Considerations, ibid. **89**: 322, 1929. (*f*) Klein, O., and Heinemann, J.: Zur Messung der Strömungsgeschwindigkeit des Blutes beim Menschen, Zentralbl. f. inn. Med. **50**:490, 1929. (*g*) Wollheim, E., and Lange, K.: Die Kreislaufzeit und ihre Beziehung zu anderen Kreislaufsgrössen, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **43**:134, 1931. (*h*) Bartels, E. C., and Powelson, M. H.: The Rate of the Circulation of the Blood in Vascular Diseases as Determined by the Use of Histamine, Proc. Staff Meet., Mayo Clin. **4**: 217, 1929. (*i*) Weiss, S.; Robb, G. P., and Blumgart, H. L.: The Velocity of Blood Flow in Health and Disease as Measured by the Effect of Histamine on the Minute Vessels, Am. Heart J. **4**:664, 1929. (*j*) Robb, G. P., and Weiss, S.: A Method for the Measurement of the Velocity of the Pulmonary and Peripheral Venous Blood Flow in Man, ibid. **8**:650, 1933. (*k*) Hitzig, W. M.: Measurement of Circulation Time from Antecubital Veins to Pulmonary Capillaries, Proc. Soc. Exper. Biol. & Med. **31**:935, 1934. (*l*) Hitzig, W. M.: The Use of Ether in Measuring the Circulation Time from the Antecubital Veins to the Pulmonary Capillaries, Am. Heart J. **10**:1080, 1935. (*m*) Candel, S.: Determination of the Normal Circulation Time from the Antecubital Veins to the Pulmonary Capillaries by a New Technic, Ann. Int. Med. **12**:236, 1938. (*n*) Blumgart, H. L.: The Velocity of Blood Flow in Health and Disease: The Velocity of Blood Flow in Man and Its Relation to Other Measurements of the Circulation, Medicine **10**:1, 1931. Footnote 1.

3. (*a*) Hirschsohn, J., and Maendl, H.: Notiz zur Kenntnis der Hämodynamik beim Pneumothorax, Beitr. z. Klin. d. Tuberk. **49**:64, 1921. (*b*) Kahler, H.: Ueber Veränderungen der Blutumlaufszeit (ein Beitrag zum Problem der Blutgeschwindigkeit), Wien. Arch. f. inn. Med. **19**:1, 1929. (*c*) Leschke, E.: Kreislaufzeit und Blutgeschwindigkeit, München. med. Wchnschr. **78**:2117, 1931. (*d*) Berinskaya, A. N., and Meerzon, T. I.: Determination of Velocity of Circulation in Functional Diagnosis of Circulation, Klin. med. **13**:1, 1935; abstracted, J. A. M. A. **104**:1680 (May 4) 1935. (*e*) Goldberg, S. J.: Use of Calcium Gluconate as Circulation Time Test, Am. J. M. Sc. **192**:36, 1936. (*f*) Spier, L. C.; Wright, I. S., and Saylor, L.: A New Method for Determining the Circulation Time Throughout the Vascular System, Am. Heart J. **12**:511, 1936. (*g*) Katz, G.: Zur Methodik der Bestimmung der Kreislaufszeit, München. med. Wchnschr. **2**:2048, 1932. (*h*) Neubauer, E., cited by Tarr, Oppenheimer and Sager.[3j]. (*i*) Winternitz, M.; Deutsch, J., and Brüll, Z.: Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufzeit mittels Decholininjektion, Med. Klin. **28**:831, 1932. (*j*) Tarr, L.; Oppenheimer, B. S., and Sager, R. V.: The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, Am. Heart J. **8**:766, 1933. (*k*) Fishberg, A. M.; Hitzig, W. H., and King, F. H.: Measurement of the Circulation Time with Saccharin, Proc. Soc. Exper. Biol. & Med. **30**:651, 1933. (*l*) Zwillinger, L.: Ueber die Magnesiumwirkung auf das Herz, Klin. Wchnschr. **14**:1429, 1935. Koch.[2a] Hitzig.[2l]

4. Loevenhart, A. S.; Lorenz, W. F.; Martin, H. G., and Malone, J. Y.: Stimulation of the Respiration by Sodium Cyanid and Its Clinical Application, Arch. Int. Med. **21**:109 (Jan.) 1918. Loevenhart, A. S.; Schlomovitz, B. H., and Seybold, E. G.: The Determination of the Circulation Time in Animals and Man, J. Pharmacol. & Exper. Therap. **15**:246, 1920.

for the determination of circulation time in man. Robb and Weiss, however, carried out the first clinical study. Since then there have been several reports.[5]

The principal site of action of the cyanide radical has been demonstrated by Heymans and his associates [6] to be the carotid bodies. Winder and his associates [7] confirmed this effect on the carotid reflex mechanism by direct injection into the carotid artery in dogs. After denervation of both sinuses, with or without double vagotomy, they found that twenty-five to seventy-five times the minimal effective dose of cyanide preceding denervation was required to produce respiratory effects after intravenous injection. A large amount of cyanide (twenty-two times the dose injected directly into the carotid artery) was required to stimulate respiration after injection into the vertebral artery. Direct injections of sodium cyanide into the fourth ventricle produced respiratory response, but the drug was definitely less effective than when injected into the carotid artery.

METHODS USED IN PRESENT STUDY

Sodium Cyanide Test.—The sodium cyanide method for determination of circulation time from the arm or the foot to the carotid sinus was used in this study. All determinations were made only after the subject had remained supine for twenty minutes or more and after his pulse rate and blood pressure had become constant. For determination of the circulation time from the arm to the carotid sinus a 2 per cent solution of sodium cyanide by weight was injected into the median

5. (*a*) Kissin, M., and Bierman, W.: Influence of Hyperpyrexia on Velocity of Blood Flow, Proc. Soc. Exper. Biol. & Med. **30**:527, 1933. (*b*) Kopp, I.: The Arm-to-Carotid Circulation Time in Prolonged Therapeutic Fever, Am. Heart J. **11**:667, 1936. (*c*) Ellis, L. B.: Circulatory Adjustments to Moderate Exercise in Normal Individuals, with Particular Reference to the Interrelation Between the Velocity and Volume of the Blood Flow, Am. J. Physiol. **101**:494, 1932. (*d*) Cohen, M. E., and Thomson, K. J.: Studies on the Circulation in Pregnancy: I. The Velocity of Blood Flow and Related Aspects of the Circulation in Normal Pregnant Women, J. Clin. Investigation **15**:607, 1936. (*e*) Robb, G. P., and Weiss, S.: The Velocity of Pulmonary and Peripheral Venous Blood Flow and Related Aspects of the Circulation in Cardiovascular Diseases: Their Relation to Clinical Types of Circulatory Failure, Am. Heart J. **9**:742, 1934. (*f*) McGuire, J., and Goldman, F.: Apparent Increased Velocity of Blood Flow in Cases of Congenital Heart Disease with Septal Defects Having Right-to-Left Shunt, ibid. **14**:230, 1937. (*g*) Youmans, J. B.; Akeroyd, J. H., Jr., and Frank, H.: Changes in the Blood and Circulation with Changes in Posture: The Effect of Exercise and Vasodilatation, J. Clin. Investigation **14**:739, 1935.

6. Heymans, C.; Bouckaert, J. J., and Dautrebande, L.: Sinus carotidien et réflexes respiratoires: III. Sensibilité des sinus carotidiens aux substances chimiques. Action stimulante respiratoire réflexe du sulfure de sodium, du cyanure de potassium, de la nicotine et de la lobéline, Arch. internat. de pharmacodyn. et de thérap. **40**:54, 1931.

7. Winder, C. V.; Winder, H. O., and Gesell, R.: The Seat of Action of Cyanide on Pulmonary Ventilation, Am. J. Physiol. **105**:311, 1933.

antecubital vein (vena mediana cubiti). The amount used was approximately 0.11 mg. for each kilogram of body weight. The level of the vein was approximately the same as that of the right auricle when injections were made; that is, the patient was supine. The needle (20 gage) was held in the vein for at least thirty seconds, so that normal venous blood flow might be established after release of the tourniquet. A stop watch was used to measure the time elapsing between the start of the rapid injection and the end point reaction. The time of injection for the arm was about one second, and that for the foot, about two seconds. Because the first reaction was a rapid dilation of the alae of the nose, followed quickly by a sharp inspiratory gasp and tachypnea, dilation of the alae was used as the end point. Approximately twice the size of the effective arm dose of sodium cyanide, or 0.22 mg. per kilogram of body weight, was needed for determination of the circulation time from the foot to the carotid sinus. If the response to injection into the median antecubital vein had been too vigorous, 1 mg. was subtracted from the quantity of sodium cyanide to be injected into the vein in the foot; if the reaction had been too weak, 1 mg. was added to it. Allowing an interval of ten minutes to elapse before repeating the dose of sodium cyanide was found to be a necessary precaution. Venipuncture in the foot was most convenient in the large vein anterior to the internal malleolus. A 24 gage needle was used for venipunctures in the foot, which also were performed with the vein at the approximate level of the right auricle. Because unforeseen reactions are possible when sodium cyanide is used, antidotes, including ampules of amyl nitrite, 10 per cent solution of sodium thiosulfate and a solution of methylthionine chloride (methylene blue), were kept at hand, and epinephrine hydrochloride was kept ready in a syringe.[8]

In our tests of circulation time we considered that the interval between injection of sodium cyanide and dilation of the alae of the nose represented the circulation time from the point of injection to the carotid sinus. Objections to this assumption were considered by Kvale, Allen and Adson.[1e] We wish to emphasize also that when circulation time is decreased the blood flows faster. The reverse is also true.

The greatest advantages of using sodium cyanide are that the response is objective and that the volume of solution to be injected is small, a distinct advantage for venipunctures in the foot. One of the greatest objections is that the persons studied often dislike the sensation of air hunger produced by the respiratory stimulation. In about 600 injections of sodium cyanide, localized venous thrombosis occurred 8 times. General systemic reactions occurred 8 times; 5 reactions were moderate, and 3 were severe. Intravenous injection of the drug is not entirely safe. We favor use of the solution of calcium and magnesium described elsewhere.[9]

Intramuscular Tension.—The method used for determination of intramuscular tension was essentially that described by Henderson, Oughterson, Greenberg and Searle,[10] except for minor modifications. In this procedure an attempt is made to measure the intramuscular pressure exerted by involuntary tone of voluntarily relaxed muscle. This is done by determining the amount of pressure,

8. Hanzlik, P. J., and Richardson, A. P.: Cyanide Antidotes, J. A. M. A. **102**:1740 (May 26) 1934.

9. Kvale, Allen and Adson.[1e] Kvale and Allen.[1d, e]

10. Henderson, Y.; Oughterson, A. W.; Greenberg, L. A., and Searle, C. P.: Muscle Tonus, Intramuscular Pressure and the Venopressor Mechanism, Am. J. Physiol. **114**:261, 1936.

measured by a water manometer, required to force physiologic solution of sodium chloride into the belly of the muscle tested. To a specially prepared 20 gage needle with a solder-filled tip and several lateral holes is attached a glass connector with a narrow lumen. These are filled with physiologic solution of sodium chloride, which makes a meniscus in the lumen of the glass connector. The needle then is inserted into the muscle through a wheal raised by the injection of procaine hydrochloride into the skin, and a U tube water manometer is attached to the glass connector by rubber tubing. The height of the column of water required to force the meniscus downward is determined and represents what is probably intramuscular tension in terms of millimeters of water. After each test the meniscus returned to its original pressure as a result of decrease of the pressure in the water manometer. Repeated determinations did not significantly influence the readings. We are not concerned in this paper with objections that muscular tone cannot be studied in this way.

TABLE 1.—*Circulation Time in Normal Subjects*

Time, Seconds	Number of Tests	
	Arm to Carotid Sinus	Foot to Carotid Sinus
10-14	7	0
15-19	29	0
20-24	34	2
25-29	13	12
30-34	3	15
35-39	0	12
40-44	0	16
45-49	0	12
50-54	0	5
55-59	0	2
60-64	0	0
65-70	0	1
Total	86	77
Average	20.1	38.7

The study of normal subjects was made in all instances on persons who had no demonstrable fault in their circulatory systems. These were chosen from among physicians, technicians and ambulatory patients, some of whom were studied before operation.

RESULTS OF STUDY OF NORMAL PERSONS

The average circulation time from the arm to the carotid sinus for 86 normal persons was twenty and one-tenth seconds, with a range of twelve and four-tenths to thirty-three and two-tenths seconds, although only 3 had a circulation time of thirty or more seconds (table 1). When the circulation time from the arm to the carotid sinus seemed too great for normal subjects, the test was usually repeated, and almost invariably the results were approximately the same. The explanation why the average arm to carotid sinus circulation time as determined in this study was greater than the average values found by others is not easy.[11] Sev-

11. Gargill, S. L.: The Use of Sodium Dehydrocholate as a Clinical Test of the Velocity of Blood Flow, New England J. Med. **209**:1089, 1933. Wood, P.: Right and Left Ventricular Failure: A Study of Circulation Time and Venous Blood Pressure, Lancet **2**:15, 1936. Robb and Weiss.[2j] Kopp.[5b]

eral factors influence circulation time, and, since the conditions of our test were not identical with those used by other investigators, it is not surprising that the results are not the same. Since there are many physiologic variations, it is well to consider that there is no normal circulation time but only a normal circulation time under a specific set of conditions. In our studies, results were discarded when the end reactions were not sharp. Determination of the foot to carotid sinus circulation time in 77 instances revealed that an average of thirty-eight and seven-tenths seconds was required. The range of values was from twenty-two to sixty-seven seconds (table 1).

TABLE 2.—*Effect of the Temperature of an Extremity on Circulation Time*

Study No.	Extremity	Surface Temperature of Fingers or Toes, C.	Circulation Time, Seconds	Pulse Rate, Beats per Minute	Oral Temperature, F.	Respirations per Minute	Blood Pressure, Mm. of Mercury	Conditions of Study
1	Right arm	31.0	25.0	60	97.4	14	84/54	Control
	Right arm	30.1	27.4	..	....	..	.....	
	Right foot	23.6	37.2	..	....	..	.....	
	Right arm	34.6	21.8	60	97.2	14	86/54	After reflex vasodilation by heat over the trunk
	Right foot	32.6	24.0	..	....	..	.....	
2	Left arm	25.6	28.6	54	97.8	14	84/56	Control
	Left foot	23.6	37.8	..	....	..	.....	
	Left arm	33.0	22.2	60	97.7	14	86/56	After reflex vasodilation by heat over the trunk
	Left foot	33.2	23.2	..	....	..	.....	
3	Right arm	24.2	36.8	54	97.2	14	88/56	Control
	Right foot	20.7	49.4	..	....	..	.....	
	Right arm	33.2	25.8	56	96.5	14	84/56	Vasodilation by 2 ounces (60 cc.) of ethyl alcohol
	Right foot	32.6	25.4	..	....	..	.....	
4	Left arm	17.8	29.2	50	97	14	104/56	Control
	Left foot	17.5	60.8	..	....	..	.....	
	Left arm	35.2	18.6	64	97.1	16	94/62	Vasodilation by heat tent over legs
	Left foot	35.6	19.8	..	....	..	.....	

CIRCULATION TIME AFTER CHANGES IN THE TEMPERATURE OF THE SKIN

A cooperative, phlegmatic, normal young man who was accustomed to laboratory procedures was the subject of this study, which was carried out in a room in which the air was maintained at constant temperature and humidity. He rested in bed until the temperature of the skin of his exposed extremities was constant. After control determinations of circulation time had been made, vasodilatation was induced reflexly by placing over the trunk a baker, the air in which was at a temperature of 55 to 60 C. This study was repeated, and on other occasions vasodilatation was induced by administration of 2 ounces (60 cc.) of ethyl alcohol and by direct application of heat to the legs. The pulse rate,

blood pressure, oral temperature and respiratory rate did not change significantly. Increase in the temperature of the skin was associated with decreased circulation time (table 2). Moreover, when the skin was warm the respiratory responses were more vigorous than when it was cold, although identical amounts of the drug were injected.

These studies appear to indicate that blood in veins flows faster when the skin is warm than when it is cold. This observation was confirmed by the studies of Kvale and his associates [9] on the circulation time in arteries. It is probable that the temperature of the skin is one of the most important regulators of speed of blood flow in the veins of the limbs. During vasodilatation the circulation time decreased from the arm and from the foot to the carotid sinus; this was effected by an increased volume flow of blood resulting from relaxation of arterioles or from opening of arteriovenous shunts. Veins do not appear to relax or dilate in the same degree, for, if they did, it appears probable that

TABLE 3.—*Effect of Exercise on Circulation Time*

	Arm to Carotid Sinus Circulation Time, Seconds			Foot to Carotid Sinus Circulation Time, Seconds		
Case	Before Exercise	After Exercise	Increase or Decrease	Before Exercise	After Exercise	Decrease
1	23.6	23.6	0	49.8	32.2	17.6
	16.0	18.8	+2.8	53.6	40.6	13.0
2	20.8	23.8	+3.0	46.4	33.2	13.2
3	17.8	19.6	+1.8	42.8	33.4	9.4

the blood would not flow faster in them when the arterioles are dilated. It seems logical to assume that if reflex dilation of veins were parallel in magnitude to that of arterioles, there should be no resultant change of circulation time from an extremity to the carotid sinus.

CIRCULATION TIME AFTER ACTIVE EXERCISE OF AN EXTREMITY

Three subjects whose ages ranged from 29 to 50 years were chosen for the tests. Preliminary determinations were made after rest in bed for forty-five to sixty-five minutes. A standard form of exercise was performed with the subject in the supine position to eliminate the influence of posture. The pulse rate was not influenced significantly by this type of exercise. Exercise of the arms consisted of moving the extended arm up and back of the head about forty times per minute and at the same time rapidly gripping the fingers into a fist and then extending them. This was continued for two minutes. The circulation time of the blood from the arm to the carotid sinus was determined within one minute after cessation of exercise. Exercise of the legs consisted of alternately lifting and dropping the leg to be tested about forty times a

minute and wiggling the foot vigorously at the same time. The tests of circulation time were performed within two minutes of cessation of exercise.

The results obtained are presented in table 3. A decrease of the circulation time from the foot to the carotid sinus occurred uniformly after exercise of the legs and varied from 24 to 40 per cent. The decrease in the circulation time from the foot to the carotid sinus as a result of exercise seems related to vasodilation, which occurs in muscle as a result of exercise.[12] The response after exercise of the arms was in contrast to this; the circulation time from the arms to the carotid sinus remained the same in 1 case and actually increased in 3. We have no adequate evidence to explain why the circulation time from the arm to the carotid sinus did not change in the same direction as that from the foot to the carotid sinus as a result of exercise. We can only assume that other factors tending to increase circulation time from the arm to the carotid sinus were not overcome by exercise of the hand and arm. Cutaneous vasoconstriction induced by elevation and exercise of the arm may have been one factor.

CIRCULATION TIME DURING ELEVATION OF AN EXTREMITY

The circulation time of 4 persons was studied. Control values were obtained after thirty to sixty minutes of rest in bed. The temperatures of the room were not controlled, but no drafts were allowed, and the lapse of time in each experiment was brief, so that the room temperature was relatively constant. With the median antecubital vein at the level of the right auricle, the circulation time from the arm to the carotid sinus was determined. The same dose of sodium cyanide was repeated eight to ten minutes later; the needle for injection was reinserted into the vein, and thirty seconds after removal of the tourniquet the arm, with the needle still in place, was elevated to an angle of about 70 degrees. Injection then was done as before. Ten minutes after a control test of the circulation time from the foot to the carotid sinus, a needle was inserted into the same vein used previously. The heel was then placed on a support of previously arranged blankets so that the leg was propped at an angle of about 30 degrees, and the test was repeated. The pulse rate did not change as a result of elevating the extremity.

12. Anrep, G. V.: Lance Medical Lectures: Studies in Cardiovascular Regulation, Stanford University, Calif., Stanford University Press, 1936, vol. 3. Kaufmann, M.: Recherches expérimentales sur la circulation dans les muscles en activité physiologique, Arch. de physiol. norm. et path. **24**:279, 1892. Krogh, A.: The Anatomy and Physiology of Capillaries, ed. 2, New Haven, Conn., Yale University Press, 1929.

Results of 5 tests on the arm and on the leg are given in table 4. In all instances definite decrease of circulation time resulted from elevation of the arms and legs. This apparently was an effect of gravity.

CIRCULATION TIME AFTER LUMBAR SYMPATHECTOMY

Studies of circulation time were made on 9 patients after surgical treatment for hypertension. Surgical treatment in all of the cases consisted of operation in two stages ten to fourteen days apart, in each of which unilateral lumbar sympathectomy and splanchnicectomy were performed.[13] The postoperative studies were done seven to thirteen days after operation. The results obtained from determinations of circulation time made preoperatively in some cases and postoperatively

TABLE 4.—*Effect of Elevation of Extremities on Circulation Time*

Case No.	Arm to Carotid Sinus Circulation Time, Seconds			Foot to Carotid Sinus Circulation Time, Seconds		
	Before Elevation	After Elevation	Decrease	Before Elevation	After Elevation	Decrease
1	23.8	20.4	3.4	46.4	35.2	11.2
2	18.8	15.0	3.8	44.0	32.8	11.2
4	17.4	14.4	3.0	42.2	37.6	4.6
	17.0	14.8	2.2	39.0	36.0	3.0
5	22.8	20.0	2.8	32.8	29.8	3.0

TABLE 5.—*Circulation Time Following Sympathectomy*

Case	Sympathectomized Side	Blood Pressure, Mm. of Mercury		Pulse Rate, Beats per Minute	Circulation Time, Seconds		
		Systolic	Diastolic		Arms to Carotid Sinus	Foot to Carotid Sinus	
						Right	Left
6	Left	222	110	84	17.6	43.6	31.8
	Both	216	104	94	13.6	42.4	46.4
7	Neither	176	122	76	20.8	63.0	....
	Both	166	116	86	....	24.8	34.6
8	Right	160	104	96	15.8	23.8	28.6
	Both	144	92	96	14.2	48.4	36.2
9	Neither	188	116	68	28.6	94.6	95.4
	Right	176	100	80	23.2	33.0	82.0
	Both	176	106	72	25.6	34.2	39.2
10	Neither	148	102	72	23.6	96.6	49.2
	Right	152	100	80	19.4	32.0	39.2
11	Neither	214	122	72	17.2	75.0	....
	Both	184	110	80	....	41.0	37.2
12	Right	210	120	84	13.6	27.0	27.4
	Both	164	106	88	....	35.2	24.0
13	Right	152	92	88	20.4	43.2	52.6
	Both	180	116	104	12.2	33.4	32.2
14	Left	170	118	96	20.0	41.2	32.0
	Both	136	90	84	....	37.8	39.6

13. Adson, A. W.; Craig, W. McK., and Brown, G. E.: Surgery in Its Relation to Hypertension, Surg., Gynec. & Obst. **62**:314, 1936. Allen, E. V., and Adson, A. W.: The Physiological Effects of Extensive Sympathectomy for Essential Hypertension, Am. Heart J. **14**:415, 1937.

in all are given in table 5. These demonstrate conclusively that lumbar sympathectomy causes a decrease in the circulation time from the foot to the carotid sinus, for in every instance in which the circulation time was determined from both feet to the carotid sinuses after unilateral sympathectomy it had decreased on the side affected by the sympathectomy (table 5). The effect of sympathectomy on circulation time is similar to that of vasodilatation, and the explanation for this seems to be the same. The temperature of the skin of the feet increased as a result of sympathectomy.

Two other observations are of interest. After both operations had been performed, the circulation time from the foot to the carotid sinus was greater on the originally sympathectomized side than it had been after the first operation and was less in the more recently sympathecto-

TABLE 6.—*Intramuscular Tension and Circulation Time After Injection of Strychnine Intramuscularly*

Strychnine, Amount Injected	Relation to Time of Injection	Intramuscular Tension of Biceps Muscle, Mm. of Water		Circulation Time, Seconds	
		Maximum	When Circulation Time Was Redetermined	Arm to Carotid Sinus	Foot to Carotid Sinus
1/20 grain.....	Before	33	...	21	63
(3 mg.)	After	122	105	25	52
1/15 grain.....	Before	38	...	20	48
(4.3 mg.)	After	113	113	22	27
1/12 grain.....	Before	45	...	16	30
(5.4 mg.)	After	100	60	17	32
1/15 grain.....	Before	10	...	34	51
(4.3 mg.)	After	98	40	19	47
1/10 grain.....	Before	8	...	22	45
(6 mg.)	After	100	50	24	43

mized side, with 1 exception (case 9). These observations suggest to us that vascular tone in limbs to which the sympathetic fibers have been cut is regained gradually.

INTRAMUSCULAR TENSION AND CIRCULATION TIME

Henderson and his associates [10] demonstrated that intramuscular injection of strychnine produces a generalized increase in intramuscular tension and concluded that this is one way to affect venous circulation. It was desirable to know the effect of strychnine on circulation time when the intramuscular tension determined by their method was increased. Accordingly, studies were made on 5 persons. After rest in bed for thirty to sixty minutes, control determinations of intramuscular tension in one biceps muscle and of circulation time were made. While the needle for determination of intramuscular tension remained in place, strychnine, varying in amounts from 1/20 to 1/10 grain (3 to 6

mg.) was injected intramuscularly into the opposite arm. The blood pressure, pulse and intramuscular tension were determined at intervals of from two to four minutes. A sharp increase in the apparent intramuscular tension began ten to fifteen minutes after the injection and increased to values approximating those obtainable by voluntary contraction of muscle. All of the 5 subjects responded to strychnine thus. The blood pressure and pulse rate were not changed significantly. At the height of the response of intramuscular tension, or as near it as was technically possible, the circulation time was determined again for the pathways from the arm and from the foot to the carotid sinus. The results are given in table 6. The circulation time from the arm to the carotid sinus was affected variably, and in only 1 instance was it decreased, but that from the foot was decreased in 4 of 5 instances. Although this decrease of circulation time was not great, it was thought to be significant because of the greatly increased magnitude of the respiratory reaction. The reactions were similar in magnitude to those which occurred when the test was performed after vasodilatation had been induced in other subjects. It was felt that the venous circulation time from the predominantly muscular lower extremities was probably decreased by the increase in intramuscular tension resulting from administration of strychnine.

CONCLUSIONS

1. The mean circulation time from the arm to the carotid sinus of normal persons in the present study was twenty and one-tenth seconds. The range was twelve and four-tenths to thirty-three and two-tenths seconds. The mean circulation time from the foot to the carotid sinus was thirty-eight and seven-tenths seconds. The range was twenty-two to sixty-seven seconds.

2. The temperature of the skin of the extremities has a prominent effect on circulation time from the foot to the carotid sinus and from the arm to the carotid sinus. Warmth of the skin decreases the circulation time, and coldness of the skin increases it.

3. Exercise of the legs decreases circulation time in the legs.

4. Elevation of an extremity decreases circulation time in the extremities.

5. Lumbar sympathectomy decreases circulation time in the legs.

6. The increase of intramuscular tension caused by strychnine tends to decrease circulation time in the legs.

CIRCULATION TIME FROM FOOT TO CAROTID SINUS AND FROM ARM TO CAROTID SINUS OF MAN

II. EFFECTS OF OPERATION AND OF ADMINISTRATION OF THYROID GLAND; POSTOPERATIVE PHLEBITIS AND PULMONARY EMBOLISM

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A description of the method used and the values for circulation time obtained with normal subjects and under various physiologic conditions have been presented in another communication.[1] The method consists of determining the time elapsing between the injection of a 2 per cent solution of sodium cyanide into an antecubital vein or into a vein of the foot and the appearance of rapid dilatation of the alae of the nose, followed by an inspiratory gasp and then by tachypnea. Ordinarily 0.11 mg. of sodium cyanide was injected for each kilogram of body weight when the circulation time from the arm to the carotid sinus was studied, and twice this amount was injected when the circulation time from the foot to the carotid sinus was studied. However, if the respiratory response was excessive when the time from the arm to the carotid sinus was determined, 1 mg. was deducted from the calculated total dose for studying the circulation time from the foot to the carotid sinus. Similarly, if the respiratory response was minimal when the circulation time from the arm to the carotid sinus was determined, 1 mg. was added to the calculated amount of sodium cyanide to be used for determination of the circulation time from the foot to the carotid sinus. In all instances the calculated time included the time required for injection, which was performed as quickly as possible. The time required was about one second for injection into a vein of the arm and about two seconds for injection into a vein of the foot. The solvent was about 0.33 cc. in volume

From the Division of Medicine, the Mayo Clinic.

1. Smith, L. A.; Allen, E. V., and Craig, W. McK.: Time Required for Blood to Flow from the Arm and from the Foot of Man to the Carotid Sinuses: I. Effect of Temperature, Exercise, Increased Intramuscular Tension, Elevation of Limbs and Sympathectomy, Arch. Surg., this issue, pp. 1366-1376.

for determination of the arm to carotid sinus circulation time and about 0.67 cc. for determination of the foot to carotid sinus circulation time. A vein at the cubital fossa and one over the internal malleolus were used for the respective tests. A 20 gage needle was used for the veins of the arm and a 24 gage needle for the veins of the foot. Reactions to injections have been noted previously.[1]

The circulation time of 31 persons was determined on the night before operations which were performed in the morning or in the morning before operations which were performed in the afternoon; the observations were repeated after operation. No attempt was made to control environmental factors, as it was desirable to study the circulation time under circumstances ordinarily present before and after operation. The 21 men and 10 women who were the basis of this study were from 31 to 68 years of age (average 48 years), of an average height of 66 inches (168 cm.) and of an average weight of 147 pounds (66.7 Kg.). It does not seem necessary to list individual values here. The average systolic blood pressure, measured in millimeters of mercury, was 123, and the average diastolic blood pressure was 71. The operations performed are listed in table 1. Determination of circulation time was made repeatedly in the course of ten postoperative days in 9 instances and in the course of thirteen postoperative days in 22 instances. Eight additional men (patients) were given desiccated thyroid gland by mouth after operation as part of a plan for preventing venous thrombosis and embolism. The averages for height, weight and age were 69 inches (175 cm.), 169 pounds (76.7 Kg.) and 50 years respectively. The operations are listed in table 2. Results of studies to determine the effects of administration of thyroid on the circulation time in cases in which operation was not performed or in which the patients were ambulatory without detectable impairment of circulation are given in table 3.

EFFECT OF OPERATION ON CIRCULATION TIME[2]

The average A-C time (table 1) determined before operation was twenty-one seconds. In the period of two to six hours after operation the A-C time decreased in 6 of the 8 cases studied (table 1). On the day following operation the A-C time was less than before operation in 2 of the cases studied (4.8 and 8.8 seconds respectively) and essentially unchanged in the other 2 cases (table 1). It is our opinion that there was a significant increase in A-C time at some time after operation in

2. For the sake of convenience the following abbreviations will be used: A-C time = time elapsing between injection of sodium cyanide into a vein at the elbow and dilatation of the alae of the nose. F-C time = time elapsing between injection of sodium cyanide into a vein of the foot and dilatation of the alae of the nose.

12 of the 31 cases studied (39 per cent). The mean of the A-C circulation times is shown in chart 1.

The average preoperative F-C time (table 1) was thirty-nine seconds. In 5 of the 9 cases studied during the postoperative period (two to six hours), the F-C time decreased significantly.[3] Two days after operation the average F-C time was greater than the average preoperative F-C time, and beginning on about the fifth postoperative day the average F-C time increased rather markedly (chart 2). Subsequently the average

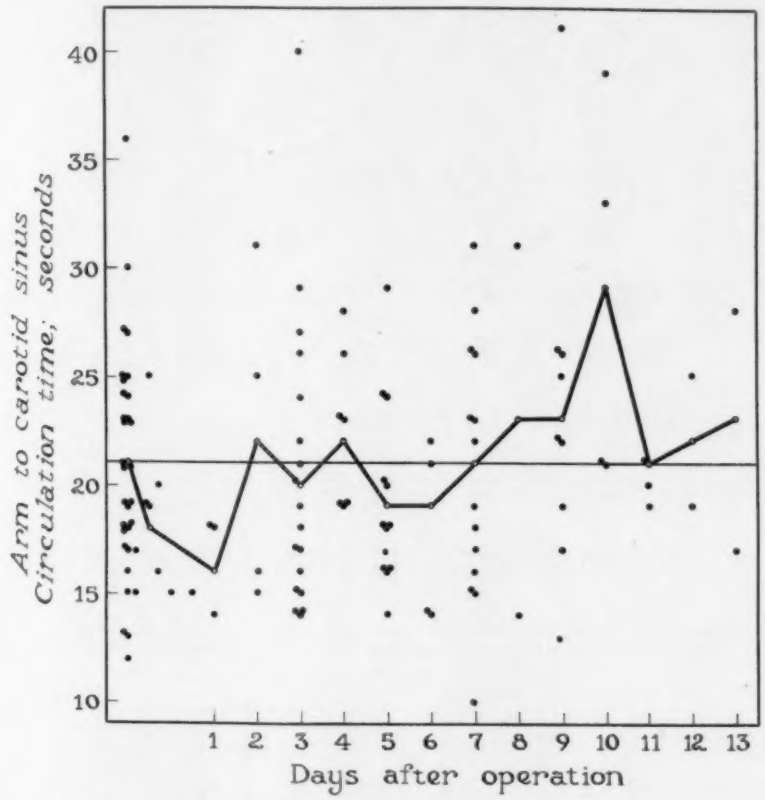

Chart 1.—Circulation time from the arm to the carotid sinus. The horizontal line shows the mean preoperative circulation time. The irregular line shows the mean circulation time at various periods.

F-C time was always greater than before operation. A study of the F-C time in individual cases, rather than the average F-C time, indicated that in 23 of 28 cases (82 per cent) the F-C time increased significantly at some time after operation (table 1).

3. We consider that an increase or decrease in A-C or in F-C time of less than four seconds is insignificant.

TABLE 1.—*Circulation Time in Cases in Which Operation Was Performed*

Case	Operation	Circulation Time, Seconds	Relation to Operation: Before	Relation to Operation: 2 to 6 Hours After	Days After Operation: 1	2	3	4	5	6	7	8	9	10	11	12	13
1	Lumbar sympathectomy *	A-C	22.6	16.0	17.8	....	....	19.4	....	....	22.6	....	....	....	....	....	....
		F-C	34.8	36.0	33.0	....	....	45.4	....	....	....	....	....	....	....	....	....
2	Cholecystectomy *	A-C	19.0	15.0	18.2	....	26.0	....	....	22.2	....	....	....	....	....	....	....
		F-C	37.6	42.4	35.4	....	52.4	....	....	....	....	....	....	....	....	....	....
3	Thyroidectomy,† B. M. R. +3%	A-C	15.6	16.6	15.0	....	....	19.0	....	24.4	....	....	....	....	....	....	....
		F-C	52.4	35.4	26.8	....	....	....	....	....	....	....	....	....	....	....	....
4	Excision of hydrocele and of lipoma of abdominal wall *	A-C	25.2	19.6	....	31.0	....	23.0	....	....	....	....	....	....	....	....	....
		F-C	50.8	45.0	....	43.0	....	54.0	....	....	....	....	....	....	....	....	....
5	Abdominal hysterectomy *	A-C	23.0	24.8	....	24.6	....	27.6	....	21.4	....	....	....	....	....	....	....
		F-C	41.2	52.0	....	....	....	....	....	....	....	....	....	....	....	....	....
6	Thyroidectomy,† B. M. R. +29%	A-C	23.2	18.8	14.4	....	....	26.4	....	....	....	....	....	....	....	....	....
		F-C	28.4	38.0	43.6	....	....	37.0	....	....	....	....	....	....	....	....	....
7	Abdominal exploration *‡	A-C	17.8	....	....	....	....	....	19.6	....	....	....	15.8	P.E.	....	....	....
		F-C	34.2	24.4	....	....	....	....	38.2	....	....	....	49.0	P.E.	....	....	....
8	Thyroidectomy,† B. M. R. +12%	A-C	21.2	13.6	....	....	....	....	....	....	....	....	....	21.2	....	....	....
		F-C	33.4	24.6	....	....	....	....	....	....	....	....	....	....	....	....	....
9	Thyroidectomy,† B. M. R. +20%	A-C	24.8	18.6	....	15.4	....	18.8	....	....	....	....	....	....	....	....	....
		F-C	40.8	29.6	....	46.8	....	32.8	....	....	....	....	....	....	....	....	....
10	Cholecystectomy *†	A-C	20.6	....	....	....	18.0	....	....	....	10.0	....	18.6	....	19.0	....	....
		F-C	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
11	Cholecystectomy, gastroduodenostomy *†	A-C	21.4	....	....	15.8	....	....	....	....	27.4	....	....	33.4	....	....	....
		F-C	41.6	....	....	36.4	....	....	....	....	57.0	....	....	....	....	....	....
12	Sigmoidotomy *‡	A-C	36.0	....	....	....	40.0	....	....	....	26.2	....	....	....	20.8	....	....
		F-C	71.2	....	....	....	58.4	....	....	....	73.6	....	....	....	42.6	....	....
13	Gastro-enterostomy *	A-C	25.2	....	....	....	....	....	24.2	....	23.2	....	....	....	20.0	....	....
		F-C	47.4	....	....	....	....	....	51.0	....	47.4	....	....	....	43.2	....	....
14	Resection of colon *†	A-C	13.4	....	....	....	14.4	....	....	....	14.8	....	....	....	....	....	....
		F-C	26.0	....	....	....	26.2	....	....	....	40.4	....	....	....	....	....	....
15	Resection of carcinoma of sigmoid *	A-C	21.2	....	....	....	....	23.2	....	....	27.6	....	26.4	....	26.4	....	....
		F-C	28.8	....	....	....	....	40.4	....	....	77.0	....	62.4	....	37.4	....	....
16	Herniotomy, excision adenomyoma *†	A-C	23.0	....	....	....	21.0	....	....	....	21.4	....	....	21.0	....	....	....
		F-C	47.0	....	....	....	....	....	....	....	60.6	....	....	76.4	....	....	....

16	Herniotomy, excision adenomyoma *†..	A-C	23.0	....	....	....	21.0	....	....	....	21.4	....	....	21.0	....	....	....
		F-C	47.0	....	....	....	....	....	....	....	60.6	....	....	76.4	....	....	....
17	Dilation and curettage cautery to cervix *	A-C	17.8	....	....	....	14.0	....	....	13.8	....	....	....	....	....	....	....
		F-C	28.6	....	....	....	....	....	....	....	....	....	....	....	....	....	....
18	Ileocolostomy *.....	A-C	13.4	....	....	....	13.8	....	14.2	....	16.4	....	13.0	....	....	....	....
		F-C	22.2	....	....	....	21.6	....	27.8	....	29.2	....	27.2	....	....	....	....
19	Resection of colon ‡.....	A-C	18.0	....	....	....	15.2	....	....	....	....	....	....	....	....	....	....
		F-C	42.0	....	....	....	19.2	....	....	....	....	....	....	....	....	....	....
20	Salpingectomy, appendectomy *.....	A-C	19.2	....	....	....	24.2	....	16.2	....	18.4	....	17.2	....	....	....	....
		F-C	28.2	....	....	....	27.4	....	23.4	....	27.2	....	33.8	....	....	....	....
21	Appendectomy, removal of ovarian cyst *	A-C	27.4	....	....	....	19.8	....	18.0	....	....	....	....	....	....	....	....
		F-C	42.4	....	....	....	....	....	....	....	....	....	....	....	....	....	....
22	Herniorrhaphy *.....	A-C	26.6	....	....	....	26.6	....	....	....	....	....	....	39.0	....	....	....
		F-C	54.0	....	....	....	78.4	....	....	....	....	....	....	83.4	....	....	....
23	Cholecystectomy *‡.....	A-C	17.2	....	....	....	....	....	14.4	....	14.4	....	....	....	....	....	....
		F-C	26.0	....	....	....	....	....	49.0	....	24.2	....	....	....	....	....	....
24	Partial gastrectomy *.	A-C	24.2	....	....	....	20.2	....	20.2	....	18.8	....	25.0	....	26.6	....	....
		F-C	46.6	....	....	....	39.6	....	44.6	....	41.2	....	39.6	....	53.0	....	....
25	Herniorrhaphy ‡.....	A-C	24.2	....	....	....	28.8	....	24.2	....	21.8	....	22.2	....	21.0	....	23.0
		F-C	32.8	....	....	....	44.8	....	53.0	....	51.8	....	66.4	....	47.4	....	67.8
26	Herniorrhaphy ‡.....	A-C	19.0	....	....	....	18.6	....	22.2	....	30.6	....	40.6	....	24.4	....	17.2
		F-C	48.4	....	....	....	33.6	....	52.0	....	62.4	....	83.2	....	68.4	....	77.4
27	Cholecystectomy *†.....	A-C	30.0	....	....	....	22.4	....	16.8	....	26.4	....	25.6	....	....	....	....
		F-C	38.2	....	....	....	38.4	....	42.2	....	50.6	....	56.8	....	....	....	....
28	Cholecystectomy, appendectomy *†.....	A-C	18.0	....	....	....	14.6	....	18.3	....	....	....	....	....	....	....	....
		F-C	31.4	....	....	....	41.2	....	55.2	....	....	....	....	....	....	....	....
29	Cholecystectomy, appendectomy *‡.....	A-C	12.4	....	....	....	15.8	....	16.0	....	14.8	....	....	....	....	....	....
		F-C	28.8	....	....	....	43.0	....	41.2	....	35.0	....	....	....	....	....	....
30	Resection of colon *‡.....	A-C	17.0	....	....	....	17.0	....	16.0	....	....	....	30.2	....	25.4	P.E. on	....
		F-C	41.8	....	....	....	38.4	....	28.2	....	....	....	46.2	....	....	22d day	....
31	Herniorrhaphy ‡.....	A-C	15.0	....	....	....	16.8	....	18.2	....	16.8	....	22.2	....	....	18.6	....
		F-C	46.8	....	....	....	54.8	....	66.0	....	60.4	....	67.4	....	....	47.2	....

* Inhalation anesthesia.
† Regional anesthesia.
‡ Spinal anesthesia.

A-C, arm to carotid sinus pathway
F-C, foot to carotid sinus pathway.
P. E., pulmonary embolism.

TABLE 2.—*Effect on Circulation Time of Administration of Thyroid Extract to Patients on Whom Operation Was Performed*

Case	Operation			Relation to Operation: Before	Days After Operation: 2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
32	Colostomy *†	C. T., seconds	A-C	24.6	....	....	21.4	....	....	....	17.8	....	....	20.6	....	....	....	....	....	....
			F-C	67.0	....	....	40.4	....	....	....	25.6	....	....	26.9	....	....	....	....	....	....
		Thyroid,‡ grains		....	..	..	..	2 (0.13 Gm.)	6	6	4 (0.26 Gm.)	6 (0.39 Gm.)	6	6	..	..	..	..	..	..
33	Abdominal exploration, carcinoma of rectum †	C. T., seconds	A-C	28.2	....	27.8	....	....	....	19.8	....	....	....	....	....	....	....	....	....	....
			F-C	30.0	....	58.4	....	....	....	....	....	....	....	....	....	....	....	....	....	....
		Thyroid, grains		....	..	..	6	6	4	6	4	..	..	..	..	..	..	..	..	..
34	Appendectomy *†	C. T., seconds	A-C	30.8	....	18.4	....	....	15.4	....	....	....	....	....	....	....	....	....	....	....
			F-C	44.4	....	52.6	....	....	30.0	....	....	....	....	....	....	....	....	....	....	....
		Thyroid, grains		....	..	6	6	6	4	2	..	..	..	..	..	..	..	..	..	..
35	Resection of ileum and half of right colon *	C. T., seconds	A-C	26.0	....	20.0	....	15.0	....	20.2	....	19.2	....	....	....	....	....	....	....	....
			F-C	44.6	....	38.0	....	31.6	....	47.0	....	45.8	....	....	....	....	....	....	....	....
		Thyroid, grains		....	2	2	2	..	4	6	6	2	..	..	..	..	..	..	..	..
36	Colostomy and exteriorization of sigmoid †	C. T., seconds	A-C	33.2	....	18.0	....	20.0	....	23.2	....	28.0	....	....	....	....	....	....	....	....
			F-C	45.2	....	57.4	....	58.6	....	39.6	....	50.2	....	....	....	....	....	....	....	....
		Thyroid, grains		....	..	4	4	6	4	3	..	..	..	..	..	..	..	..	..	..
37	Gastro-enterostomy *	C. T., seconds	A-C	18.6	....	....	20.4	....	13.8	....	15.0	....	24.6	....	....	....	....	....	....	....
			F-C	30.0	....	....	37.6	....	36.4	....	32.6	....	34.2	....	....	....	....	....	....	....
		Thyroid, grains		....	..	..	6	6	6	6	6	..	..	..	..	..	..	..	..	..
38	Cholecystectomy *	C. T., seconds	A-C	22.4	....	18.0	....	19.8	....	16.0	....	23.6	....	15.4	....	....	....	....	....	....
			F-C	48.4	....	33.0	....	39.4	....	35.2	....	43.0	....	32.6	....	....	....	....	....	....
		Thyroid, grains		....	..	..	6	6	6	6	6	6	6	..	..	..	..	..	..	..
39	Repair of ventral hernia †	C. T., seconds	A-C	20.6	....	17.2	...	21.4	....	20.4	....	20.6	....	20.8	....	....	20.2	....	....	20.6
			F-C	51.0	....	52.8	....	35.4	....	36.6	....	32.4	....	37.0	....	....	49.4	....	....	39.6
		Thyroid, grains		....	4	6	6	6	6	6	6	6	6	6	6	4	4	6	2	..

* Inhalation anesthesia.
† Spinal anesthesia.
‡ Desiccated thyroid gland.

A-C, arm to carotid sinus pathway.
F-C, foot to carotid sinus pathway.
C. T., circulation time.

Because the circulation time was not determined at the same time in relation to operation in all of these cases, we selected the results of study of circulation time in a second group of subjects for reconsideration because there was fair uniformity of relation of the time of the test to operation in these cases, because studies were carried out over sufficiently long periods and because major operations had been performed. In addition, we excluded instances of hyperthyroidism, which in itself might

TABLE 3.—*Effect on Circulation Time of Administration of Thyroid Extract to Normal Subjects*

Case	Day	Thyroid Extract, Grains	Circulation Time		Pulse Rate
			A-C *	F-C †	
40	..	0	22	35	66
	1	4	..	..	..
	2	6	24	39	76
	3	6	18	37	80
	4	4	17	27	84
	5	2	19	34	70
41	..	0	20	45	66
	1	4	..	..	..
	2	6	24	65	72
	3	6	15	60	72
	4	4	20	39	84
	5	2	16	38	82
42	..	0	22	42	72
	1	4	..	..	..
	2	6	24	52	80
	3	6	18	31	84
	4	6	18	32	84
	5	0	17	30	80
	6	0	22	29	84
	7	0	23	38	84
	8	0	23	36	80
	9	0	23	41	80
43	..	0	18	35	72
	1	4	..	..	..
	2	6	21	45	84
	3	6	19	40	80
	4	6	14	29	90
	5	0	14	31	84
	6	0	21	29	88
	7	0	22	39	90
	8	0	19	28	84
	9	0	20	37	72

* Arm to carotid sinus time in seconds.
† Foot to carotid sinus time in seconds.

influence circulation time, and cases of sympathectomy, which might influence the circulation time specifically. The 10 cases in this group presented characteristic examples of rather routine major surgical procedures (cases 18, 19, 23, 24, 25, 26, 27, 29, 30 and 31, table 1). The influence of operation on circulation time is illustrated strikingly in chart 3. The average A-C time remained essentially unchanged in this group until the ninth postoperative day, when it increased about five seconds from a preoperative average value of nineteen and one-tenth seconds. The F-C time increased regularly from thirty-three and three-

† Spinal anesthesia.
‡ Desiccated thyroid gland.

tenths seconds before operation to fifty-six and one-tenth seconds on the eleventh postoperative day.

These studies indicate to us several interesting changes in the speed of blood flow in veins of the extremities after operation.[4] The decreased circulation time noted shortly after operation apparently results from the vasodilating effect of anesthesia and of fever and possibly from

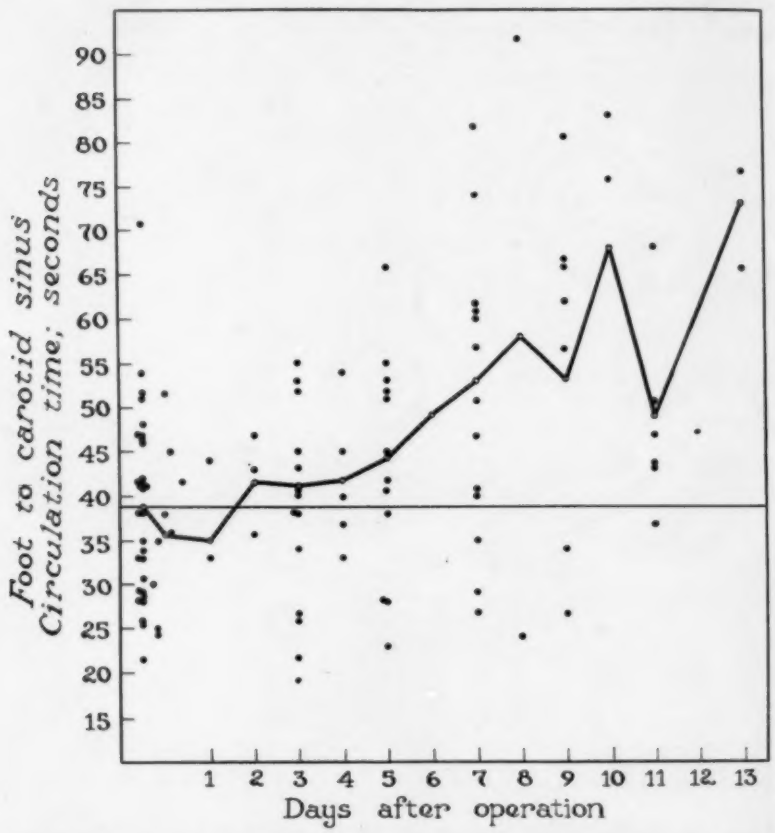

Chart 2.—Circulation time from the foot to the carotid sinus. The horizontal line shows the mean preoperative circulation time. The irregular line shows the mean circulation time at various periods.

4. We are aware that the test indicates the rate of circulation in the veins of the extremities and in the heart and pulmonary circulation. We believe that changes in circulation time noted in these studies, however, are a measure of changes in rate of circulation in peripheral veins. This belief is supported by the data summarized in chart 3. The A-C time changed little, and the F-C time changed much. If these changes were due to changes in rate of circulation in the heart and lungs, the A-C and F-C times should have changed similarly.

tachycardia. The cause of increases in circulation time which occur subsequently will be considered later.

GENERAL CONSIDERATION OF RELATIONS OF CIRCULATION TIME TO POSTOPERATIVE VENOUS THROMBOSIS AND PULMONARY EMBOLISM

From the beginning of the study it was obvious that the postoperative changes in the F-C time, which usually were marked, would be of much greater interest than the changes in the A-C time, which usually were not marked (table 1; charts 1, 2 and 3). This observation seems to have definite significance when applied to the problem of postoperative pulmonary embolism. It is very rare for thrombophlebitis or venous thrombosis to occur in the veins of the arms postoperatively. Conversely,

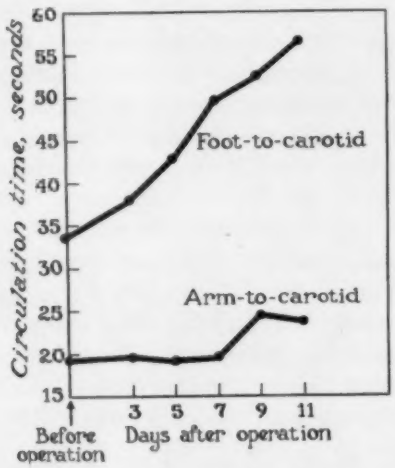

Chart 3.—Circulation time from the arm to the carotid sinus and from the foot to the carotid sinus in a selected group of patients (see text).

thrombophlebitis and thrombosis leading to embolism usually occur in veins of the lower extremities or of the pelvis. It seems more than a coincidence that the apparent average time after operation at which thrombosis in these locations occurs corresponds to the period at which F-C time is great when contrasted with the preoperative circulation time. That phlebitis and venous thrombosis occur seldom in the veins of the arms seems less strange with the knowledge that the A-C time is usually little changed postoperatively. The implication is that slowing of venous circulation contributes to thrombophlebitis and venous thrombosis in the lower extremities. We cannot emphasize that failure of venous circula-

tion to slow prevents these complications from occurring commonly in the upper extremities, for it does slow sometimes (table 1), although not as much or as frequently as it does in the legs.

In the analysis of postoperative embolism, the figures of Barker and his co-workers [5] show that, while pulmonary emboli occur from the first to later than the twenty-fifth postoperative day, the highest incidence is from the sixth to the twelfth postoperative day. In the study of Barker and his co-workers [6] the highest incidence for postoperative embolism was noted on the eleventh postoperative day. It seems that the crux of the situation lies in the question as to when the thrombosis or extension of clot formation which leads to embolism has occurred. It seems true that if a thrombus remains in the femoral vein for as long as twenty-four hours there may be signs of beginning organization, which might be observed microscopically.[7] It has also been observed that in necropsies of patients with fatal pulmonary emboli it is often difficult to find the site of thrombosis. This would not be true if there had been organization of the clot. Moreover, examination of the embolus for signs of organization is almost invariably fruitless.[7] These facts would seem to indicate that the thrombus or the propagated portion of thrombus which broke loose to become an embolus was actually formed only a short time before pulmonary embolism occurred, probably within twenty-four hours before the embolism occurred. Hence it was formed at a time when the circulation time from the foot to the carotid sinus is usually increased.

We consider that there are three possible causes for phlebitis and venous thrombosis following operation: (1) increased tendency of blood to clot; [8] (2) injury to the intima of veins which serves as a locus for phlebitis or venous thrombosis,[9] and (3) slowed circulation in veins.[10]

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5. Barker, N. W.; Nygaard, K. K.; Walters, W., and Priestley, J. T.: Unpublished data.

6. Fifty per cent of instances of postoperative pulmonary embolism occurred from the seventh to the fifteenth postoperative day.

7. Robertson, H.: Personal communication to the authors.

8. Allen, E. V.: Changes in the Blood Following Operation, Arch. Surg. **15**:254-264 (Aug.) 1927. Dawbarn, R. Y.; Earlam, F., and Evans, W. H.: The Relation of the Blood Platelets to Thrombosis After Operation and Parturition, J. Path. & Bact. **31**:833-873 (Oct.) 1928. Belt, T. H.: Thrombosis and Pulmonary Embolism, Am. J. Path. **10**:129-144 (Jan.) 1934.

9. Edwards, E. A.: Observations on Phlebitis, Am. Heart J. **14**:428-441 (Oct.) 1937. Cohnheim, J.: Lectures on General Pathology, London, New Sydenham Society, 1889, vol. 1, p. 172.

10. (*a*) Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, 1924, chap. 11, pp. 253-278. (*b*) Brown, G. E.: Postoperative Phlebitis: A Clinical Study, Arch. Surg. **15**:245-253 (Aug.) 1927. (*c*) Walters, W.: A Method of Reducing the Incidence of Fatal Postoperative Pulmonary Embolism: Results of Its Use in Four Thousand and Five Hundred Surgical Cases, Surg., Gynec. & Obst. **50**:154-159 (Jan.) 1930.

If increased tendency of the blood to clot were the sole cause of phlebitis and venous thrombosis, these should occur at any place in the body. Actually they occur selectively, chiefly in the lower extremities. However, intimal changes may have been present before operation in the veins of the legs, so that the tendency to thrombosis may be greater at this site. If the sole cause were damage to the intima of veins occurring at the time of operation, phlebitis and venous thrombosis should not occur after such operations as gastroenterostomy, for example, during which injury to the veins of the legs and of the pelvis presumably does not occur. Actually, venous thrombosis and pulmonary embolism occur after such operations. It may be significant, however, that the incidence of postoperative embolism is more than twice as great after hysterectomy as after cholecystectomy, which may indicate that damage to veins may be important in causing thrombosis leading to embolism in many cases (Barker and his co-workers [5]). If slowed venous circulation in the legs were the sole cause of phlebitis and venous thrombosis, perhaps they ought to occur much more frequently than they do, since the circulation in the veins of the legs slows at some time after operation in about 82 per cent of instances, whereas the incidence of postoperative venous thrombosis and pulmonary embolism following laparotomy is only about 2 per cent.[5]

We do not wish to imply that slowed venous circulation is the sole cause for phlebitis and venous thrombosis, for apparently it is not, but we do think that it is an important factor, and it may be of primary importance. All the factors mentioned previously may be important, and we are less interested in determining their comparative importance than in emphasizing that slowed venous circulation in the legs and, less remarkably, in the arms does occur after operation and that it seems to contribute importantly to the genesis of postoperative phlebitis and venous thrombosis. If it is justifiable to assume that slowed venous circulation is important in the genesis of postoperative venous thrombosis, it is important in consideration of pulmonary embolism following operation, since embolism originates from a clot in a vein involved by inflammation or by simple thrombosis. Naturally, individual cases of phlebitis, venous thrombosis or pulmonary embolism occurring at a time (within the first two days after operation, for example) when there seems to be no significant increase in F-C time cannot be accounted for by changes in the rate of venous circulation. Under such circumstances other factors are obviously more important.

It has been amply proved [11] that blood flow through an extremity varies widely. Recognition of the great influence of such factors as

11. Freeman, N. E.: The Effect of Temperature on the Rate of Blood Flow in the Normal and in the Sympathectomized Hand, Am. J. Physiol. **113**:384-398 (Oct.) 1935. Youmans, J. B.; Akeroyd, J. H., Jr., and Frank, H.: Changes in the

(Footnote continued on next page)

temperature, exercise and position on the circulation time makes it apparent that there can really be no constancy of circulation time. As a matter of fact, it is impossible to obtain a true average circulation time unless it is an average for a stated set of conditions. It is not surprising, therefore, that venous circulation changes after operation. The difference in the influence of operation on A-C and on F-C time may depend on many things. Probably the two most important factors are (1) the difference in activity and in elevation of the arms and legs and (2) the temperature of the skin.

Many more movements are made with the arms than are made with the legs postoperatively. Repeated elevation of the hands above the level of the heart occurs. The legs are almost always below the level of the heart, and this situation is accentuated when the patient sits in bed, as he does during a good deal of his convalescence. We have shown [1] that elevation of extremities increases the rate of circulation in the veins of the arms. Exercises which we had our patients perform specifically for the purpose of studying the effect of exercise on the rate of venous circulation effectively decreased the F-C time but did not modify the A-C time significantly. This phase of the problem needs further consideration.

Moreover, the temperature of the skin of the toes is almost always less than that of the fingers. We have shown [1] that blood flows slowly in the veins of the extremities when the skin is cold and rapidly when the skin is warm.

If an attempt were made to depict the course of postoperative events in many cases (but not in all), the picture would probably be somewhat as follows. The patient who has had an operation for which a general anesthetic has been used returns to his room in good condition, with warm, flushed extremities and hence with faster blood flow in the peripheral veins (table 1). The cardiac output [12] is increased, and this

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Blood and Circulation with Changes in Posture: The Effect of Exercise and Vasodilatation, J. Clin. Investigation **4**:739-753 (Nov.) 1935. Ellis, L. B.: Circulatory Adjustments to Moderate Exercise in Normal Individuals, with Particular Reference to the Interrelation Between the Velocity and Volume of the Blood Flow, Am. J. Physiol. **101**:494-502 (Aug.) 1932. Kvale, W. F.; Smith, L. A., and Allen, E. V.: Speed of Blood Flow in the Arteries and in the Veins of Man, Arch. Surg. **40**:344-351 (Feb.) 1940. Smith and others.[1]

12. Blalock, A.: Cardiac Output in the Dog During Ether Anesthesia: I. The Effect of Ether Anesthesia on the Cardiac Output, Arch. Surg. **14**:732-751 (March) 1927. Snyder, J. C.: The Cardiac Output and Oxygen Consumption of Nine Surgical Patients Before and After Operation, J. Clin. Investigation **7**:571-579 (Sept.) 1938. Polano, H.: Experimentelle Untersuchungen über das Verhalten des Minutenvolumens des menschlichen Herzens bei Äthernarkose, Lumbalanästhesie und nach operativen Eingriffen (Bestimmung des Minutenvolumens nach Broemser), Deutsche Ztschr. f. Chir. **239**:505-513, 1933.

presumably increases the rate of flow of blood in the peripheral veins. This decrease of circulation time is contributed to by the common use of hot water bottles, elevation of the foot of the bed and restlessness of the patient.

On the second postoperative day the circulation time is about the same as it was before operation, and, provided there is not considerable fever, the F-C time begins to increase gradually. This may be because the patient soon sits up in bed, likes his room cooler, may begin smoking cigarets and becomes annoyed at slight discomforts and because removal of hot water bottles may allow his feet to remain cool or cold. Muscle tone may decrease.[13] Presumably all these things increase the circulation time, because venous blood seems to flow more slowly "uphill" and because cool environmental temperature, annoyance and cigaret smoking cause coolness of the skin, which appears to slow the flow of blood in veins. Disappearance of fever and return of cardiac output and pulse to normal allow slowing of venous circulation. Perhaps cessation of sedation and of intravenous injection of fluids may influence the circulation time. During this time, when more attention to his venous circulation is needed, the patient ordinarily receives none. A few days before he plans to leave the hospital, at a time when the circulation in the veins is markedly slowed, thrombophlebitis may occur, or a bland clot may form in a vein. When the patient becomes active, perhaps only to the extent of dangling the feet, or before this time, the clot becomes an embolus, or parts of it may separate from the vein and cause pulmonary embolism. Again, we wish to emphasize that we do not believe that increased circulation time is solely responsible for venous thrombosis.

If a maximal effort is to be made to prevent thrombophlebitis and venous thrombosis after operation, attempts should be made to reduce coagulation of the blood, to prevent injury to veins and to prevent slowing of the flow of blood in the veins of the legs. The first can be accomplished by injecting heparin intravenously; but heparin is expensive, the technic of administration is comparatively complex and discomfort occasioned by continuous intravenous administration is not negligible. This should be a reliable method of preventing postoperative venous thrombosis, although evidence is not conclusive on this point yet, as far as we know. Apparently nothing more can be done about the question of injury to veins than has already been accomplished by careful surgical technic. If roughening of the intima of veins in the legs exists before operation, nothing can be done to restore the intima to normal. It may be comparatively easy to increase the speed of flow

13. Incomplete studies indicate that intramuscular tension decreases postoperatively in some cases. This may cause increased circulation time.[1]

of blood in veins of the extremities after operation, and this phase of the problem deserves further study. Theoretically, keeping the feet warm, exercise of the legs or a recumbent position with the foot of the bed elevated should prevent slowing of venous circulation after operation. We believe that the importance of increased circulation time in the genesis of postoperative venous thrombosis and pulmonary embolism can actually be determined in only one way, by preventing the decrease in speed of circulation in veins in a sufficiently large number of cases to determine the influence of this procedure on the incidence of venous thrombosis.

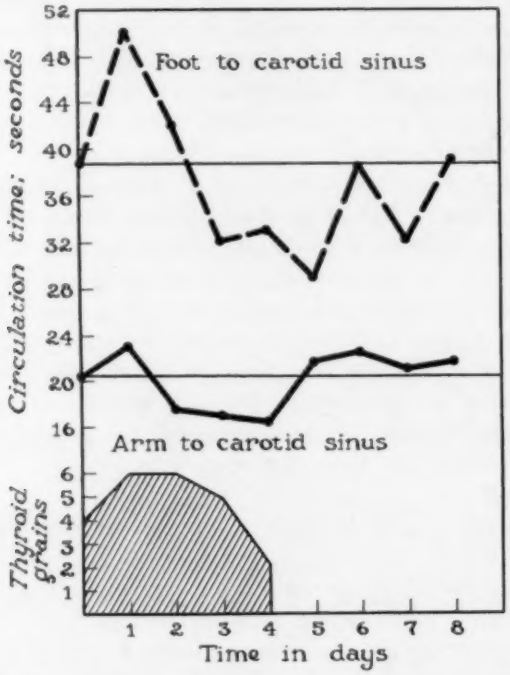

Chart 4.—Effect of administration of thyroid on the circulation time in subjects on whom operation had not been performed.

EFFECT OF ADMINISTRATION OF THYROID GLAND

Normal Subjects.—Administration of thyroid gland decreases the circulation time, although at the end of a twenty-four hour period after beginning administration of it there is evidence of an increase. In our studies of 4 patients, decrease of the average A-C time was noted forty-eight hours after beginning a program of daily administration of thyroid, and decrease of the average F-C time was noted seventy-two hours after beginning such a program (table 3, chart 4). When administration

of thyroid was stopped, the A-C time of the only 2 patients on whom study was continued was normal in twenty-four hours. The average F-C time continued to decrease for twenty-four hours after cessation of administration and did not reach the value noted before administration until two to five days after cessation (table 3). The decreased venous circulation time which results from administration of thyroid seems to be brought about by tachycardia and vasodilatation.

Subjects After Operation.—Thyroid extract was administered in doses of 2 to 6 grains (0.13 to 0.4 Gm.) daily, beginning two to five days postoperatively,[14] and reaching a maximum average dose between the second and the eighth postoperative day. The blocked curve representing the amount of thyroid administered to patients receiving it was obtained by averaging the amounts of thyroid for each postoperative day (chart 5). The average preoperative A-C time of twenty-five and eight-tenths seconds and the average preoperative F-C time of forty-two and five-tenths seconds were greater than the average normal values for these circulation times, probably because the patients were sick. The average circulation time for this group of patients did not increase after operation as it did in a group of patients who did not receive thyroid (charts 1, 2 and 3). The tendency of the curves to rise to the average preoperative level in the latter part of the study may have been the result of failure of reduced amounts of thyroid to offset the usual tendency for the F-C time to increase. Of greatest interest is the fact that the average A-C time and the average F-C time were less than the average preoperative circulation times throughout the period of convalescence, with 1 exception.

Analysis of the results in individual cases shows that the A-C time was rarely significantly greater after operation than before operation. In case 34, the F-C time was greater on the third postoperative day than before operation, but thyroid medication had been begun only on the third postoperative day. In case 36, the F-C time was greater on the third, fifth and ninth postoperative days (thyroid medication was begun on the third postoperative day). In case 37, the F-C time was persistently greater after operation than it was before operation, in spite of administration of thyroid. With the exceptions just noted the F-C time was not significantly greater after postoperative administration of thyroid was begun. The analysis of individual results emphasizes the errors which may result from using average values, which in this instance erroneously indicate that the F-C time did not increase after operation. It is obviously inadvisable to conclude that administration of thyroid prevents the increase in F-C time ordinarily noted following operation. However, our incomplete study indicates that it tends to

14. The day of operation is considered the first postoperative day.

produce such a result.[15] It is quite apparent that circulation time would not be influenced by thyroid administered on the same day on which a study of the circulation time was carried out. In considering the relation of postoperative administration of thyroid to circulation time and pul-

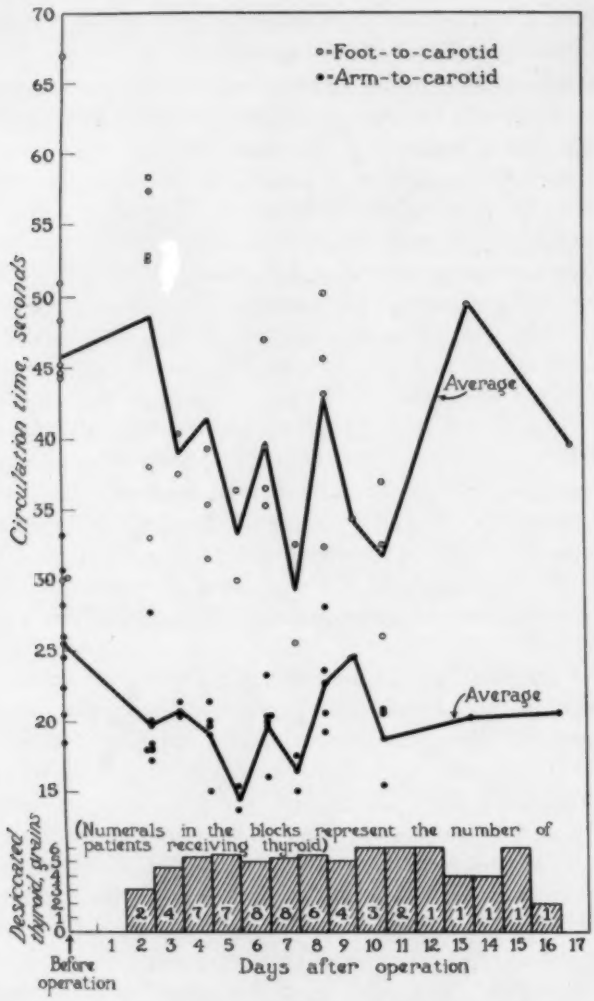
Foot-to-carotid
Arm-to-carotid
Average
Average
Circulation time, seconds
Desiccated thyroid, grains
(Numerals in the blocks represent the number of patients receiving thyroid)
2 4 7 7 8 8 6 4 3 2 1 1 1 1 1
Before operation
Days after operation

Chart 5.—Effect of administration of thyroid on the circulation time in subjects on whom operation had been performed.

monary embolism, it is important to consider the time of administration and the amount of thyroid and to bear in mind that in spite of judicious administration the venous circulation time may increase postoperatively.

15. The report by Walters [10c] that postoperative administration of thyroid gland diminishes the incidence of pulmonary embolism is important.

One should bear in mind that it is insufficient simply to administer thyroid after operation. One must know whether administration of it prevents slowing of venous circulation.

CONCLUSIONS

1. After operation the circulation time from the foot to the carotid sinus is usually increased after the fourth postoperative day, that is, blood flows more slowly. Increases in the circulation time from the arm to the carotid sinus are less common and less marked. The slowing of venous circulation probably is an important factor in the complicated mechanism of postoperative venous thrombosis and pulmonary embolism.

2. Administration of thyroid gland to normal subjects decreases circulation time, that is, increases the rate of flow of blood from the arm and from the foot to the carotid sinus. Postoperative administration tends to prevent the slowing of venous circulation which occurs commonly after operation.

REVASCULARIZATION OF THE ISCHEMIC KIDNEY

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The recent contributions of Goldblatt and his associates [1] have placed renal ischemia as a cause of hypertension in the center of interest. When the ischemic tissue was removed or when circulation was reestablished, the experimental hypertension disappeared. Goldblatt [2] made the significant observation that "if before constricting the renal artery the kidney is decapsulated and adipose or muscle tissue is attached to the denuded cortical surfaces, the accessory circulation from the adherent tissues becomes very prominent and interferes with the development of pronounced elevation of blood pressure." Animals survive complete closure of both main arteries "when effected gradually by increasing the constriction at intervals. This is proof that such accessory circulation can be functionally highly effective." Verney and Vogt [3] have observed that collateral circulation through the capsule or the hilus of the kidney may be sufficient to restore the increased blood pressure to normal in an animal with clamped renal vessels; they also found that extirpation of this collateral circulation raises blood pressure.

One of us (G. de T.) has been stimulated to experimental and clinical research on this problem by the investigations of Paunz,[4] undertaken at the University of Budapest, Hungary, between the years 1926 and 1930. This author first showed that an omental graft to the kidney

From the Circulatory Group, St. Luke's Hospital, and the Department of Surgery, University of Illinois, College of Medicine.

1. Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension: I. The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, J. Exper. Med. **59**:347, 1934.

2. Goldblatt, H.: Experimental Observations on the Surgical Treatment of Hypertension, Surgery **4**:483, 1938.

3. Verney, E. B., and Vogt, M.: An Experimental Investigation into Hypertension of Renal Origin with Some Observations on Convulsive Uremia, Quart. J. Exper. Physiol. **28**:253, 1938.

4. Paunz, L.: Die Inversion des Nierenkreislaufes, Ztschr. f. d. ges. exper. Med. **52**:548, 1926; Die Ersetzung der Vena renalis durch künstlich hervorgerufene Netzanastomosen, ibid. **59**:391, 1928; Die Erzeugung einer doppelten Blutkreislaufes in der Niere, ibid. **59**:280, 1928; Dauerversuch über die Ersetzung der Arteria renalis durch künstlich hervorgerufene Netzanastomosen, ibid. **71**:321, 1930.

could effectively drain venous circulation when the renal vein was obstructed; later he found that if he decapsulated and wrapped up one kidney in omentum, tied the renal artery of the same side one month later and subsequently removed the other kidney, the dog survived as long as one year, excreted 200 to 300 cc. of urine daily, had normal concentrating and diluting power and showed only traces of albumin. When the animal was killed in perfect health, vascular granulations were found between the omentum and the scarified cortex of the kidney, but no dense scar tissue had formed. He kept a series of 18 dogs alive for varying periods. Recently MacNider and Donnelly,[5] using a similar technic of omentopexy, studied the growth of capillary buds in the normal kidney; they found them around the convoluted tubules but not in the vicinity of the glomeruli. The omental vessels showed hyperplasia of their walls as if increased blood flow had taken place through them. Davis and Tullis[6] placed omentum into the decapsulated and longitudinally split normal kidneys of dogs and later divided the renal vessels on the same side. The vascularization of the side operated on proved to be much greater than that of the control side; also the functional capacity of the operatively treated kidney seemed greater, as studied by the dye excretion and urea clearance tests. Mansfield, Weeks, Steiner and Victor[7] found that Goldblatt hypertension was reducible by implants of omentum or spleen into the kidney. The splenopexy gave longer lasting effects because of a greater development of collateral circulation. Goldberg, Rodbard and Katz,[8] however, could not obtain lowering of Goldblatt hypertension when they brought decapsulated kidneys into contact with denuded muscle; on the contrary, heavy scar tissue was found in the place of the renal capsule.

In unpublished and incomplete experiments undertaken between 1933 and 1936, Slaughter, Karstens, Bedinger and one of us (G. de T.) injected 10 per cent sodium morrhuate into the left renal artery and produced a small fibrous kidney within a month; this kidney was then decapsulated, scarified and wrapped in omentum; a month later, the right kidney was removed. Because of the variable response to the sclerosing solution and the presence of aberrant vessels, uniform atrophy

5. MacNider, W. de B., and Donnelly, G. L.: Value of Omentopexy in Establishing an Adventitious Circulation in the Normal Kidney, Proc. Soc. Exper. Biol. & Med. **40**:271, 1939.

6. Davis, H. A., and Tullis, I. F., Jr.: The Effect of the Experimental Production of an Accessory Blood Supply upon Normal Kidney, Proc. Soc. Exper. Biol. & Med. **40**:161, 1939.

7. Mansfield, J. S.; Weeks, D. M.; Steiner, A., and Victor, J.: Reduction of Experimental Renal Hypertension by Pexis of Spleen or Omentum to Kidney, Proc. Soc. Exper. Biol. & Med. **40**:708, 1939.

8. Goldberg, S.; Rodbard, S., and Katz, L.: Increased Collateral Blood Supply to the Kidney in Renal Hypertension, Surgery **7**:869, 1940.

could not be produced. Because of technical difficulties and especially because of Goldblatt's outstanding contribution to the production of uniform hypertension, these experiments were discontinued in 1936. Nevertheless, it was felt that these experiments more closely imitated arteriolar sclerosis in the kidney than did obstruction of the main artery, and the results were encouraging enough at the time to lead us to try renal revascularization on certain patients suffering from renal vascular damage.

Our first patient, Alma J., was operated on in April 1936, at which time muscle flaps were sutured around the decapsulated and scarified kidney on both sides. Since that time, 2 more patients (cases 3 and 4) have had a similar operation, but unilaterally; in case 2, omentum was used to cover the kidney.[9] Recently (January 1939) Abrami, Iselin and Wallich [10] reported 1 case of chronic glomerulonephritis and another of malignant nephrosclerosis in which unilateral omental transplants were done; both cases were reported within three months of the operation, and no results were obtained.

REPORT OF CASES

Case 1.—In April 1936, Alma J., a pale, thin woman aged 39, was referred to the neurocirculatory clinic at St. Luke's Hospital by Dr. Thomas J. Fentress. She complained of severe headaches, ringing in the ears, blurred vision and extreme nervousness. She had not been seriously ill until the age of 35, when her blood pressure was first examined because of frequent headaches. The systolic blood pressure dropped from 285 to 158 mm. of mercury after three months of rest in bed. Again, in January 1933, her blood pressure reached 250 mm. of mercury. On examination at the Mayo Clinic, in April 1934, her blood pressure was 252 mm. of mercury systolic and 140 diastolic. A report obtained of her status then revealed a normal blood count, a negative reaction for syphilis and a value for blood urea of 38 mg. per hundred cubic centimeters. An electrocardiogram showed a rate of 72, sinus rhythm, a slurred QRS complex in derivation III, left ventricular preponderance, diphasic P waves in lead IV and inverted T waves in leads II and III.

Physical examination disclosed slight left ventricular hypertrophy, with forceful pulsation at the apex, and hyperactive reflexes of the left upper extremity, with fleeting paralysis. There was papilledema of 3 D. on the right and 2 D. on the left. The retinal vessels were constricted and tortuous. There were no hemorrhages or exudates (Dr. Frank Brawley). The concentration-dilution test showed the specific

9. A fifth patient, a 7 year old girl, was operated on in February 1940, omentum being used on one side and a pedicled muscle flap on the other. This child had bilateral congenital hypoplasia of both kidneys, producing severe hypertension. The case will be reported in detail after a longer period of observation. Six months after the operation the child was free of headaches and dizziness and gained strength and weight. A bilateral transdiaphragmatic splanchnic section has been performed in addition.

10. Abrami, P.; Iselin, M., and Wallich, R.: Essai de traitement de l'hypertension artérielle, d'origine rénale par la révascularisation chirurgicale du rein (néphro-omentopexie), Presse méd. **47**:137, 1939.

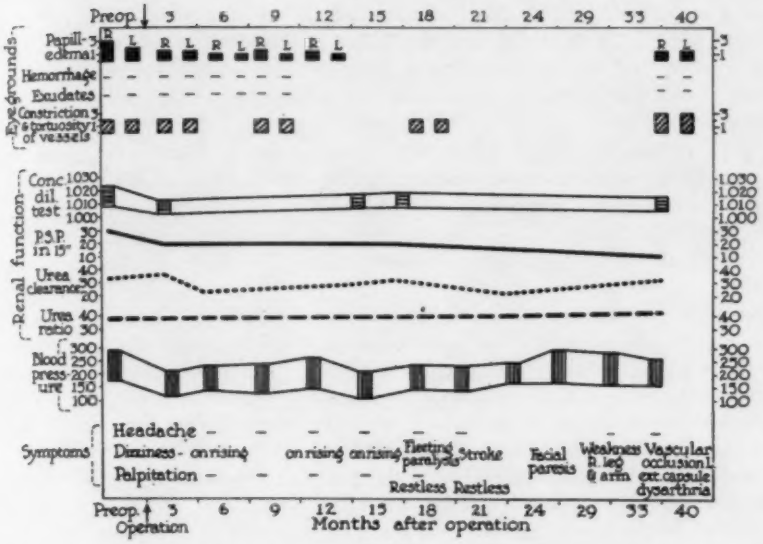

Fig. 1.—Preoperative and postoperative records of Alma J., 39 years old. During a postoperative course of forty months the eyegrounds showed no significant change except fluctuations in papilledema, which is not easy to measure accurately. In spite of repeated cerebral vascular accidents, no retinal hemorrhages or perivascular exudates were seen; constriction and tortuosity of the retinal vessels were measured on the basis of 1 plus to 4 plus. The specific gravity of the urine varied from 1.025 just prior to operation to its lowest figure, 1.013, three months after the operation. At the end of forty months, the specific gravity was 1.016. Dilution varied from 1.004 at three months, to 1.008 at twelve months, which was also a preoperative figure. The fifteen minute excretion of phenolsulfonphthalein was 30 per cent prior to operation and 20 per cent at three months and twelve months after operation; it declined to 10 per cent at last examination. The standard urea clearance of 33.8 cc. of blood per minute fluctuated slightly during the postoperative course but was still 31.2 cc. per minute at the forty month observation. The urea ratio ($\frac{\text{urea N} \times 100}{\text{N.P.N.}}$) was 37 preoperatively, remained the same three months later, rose slightly to 39 at the end of the twenty-first month and was 43 at the end of forty months. The blood pressure varied from the maximum of 300 systolic and 170 diastolic at the twenty-fourth month, during an acute attack of hypertensive encephalopathy, to the minimum of 214 systolic and 140 diastolic fifteen months after operation. Of the subjective symptoms prior to operation, dizziness on rising always persisted; after a vascular accident occurring thirty months postoperatively, weakness in the right arm and leg became pronounced. The chart shows a slight but definite progress in renal damage indicated by the fifteen minute phenolsulfalein test, the concentrating ability and the urea ratio; the heart remained remarkably unaffected during this period. The hypertensive encephalopathy progressed from a prodromal symptom of fleeting paralysis in one arm to massive vascular occlusion in the external capsule on the left; this will probably cause death.

gravity of the urine to be from 1.008 to 1.025. The rate of phenolsulfonphthalein excretion was 30 per cent in fifteen minutes and 65 per cent in two hours. The urea ratio was 37. A diagnosis of severe benign nephrosclerosis was made.

On April 9, 1936, through a lumbar incision and with resection of the tip of the twelfth rib, the left kidney was exposed. It was small and firm and showed depressed scars over the cortex. Decapsulation was easy. The cortex was scarified with a scalpel; a pedicled flap of the musculus quadratus lumborum, 8 cm. in length and 3 cm. in width, was swung around the kidney and anchored with a few interrupted sutures. Closure was made with an all-silk technic, in layers.

On April 20 an identical exposure was made and the same procedure was done on the right side. The right kidney seemed somewhat larger and softer than the left.

Uneventful convalescence followed this two stage operation. Subjectively, headaches, heart consciousness and dizziness disappeared and did not recur. Dizziness returned ten months after the operation, but only on rising suddenly. A year after operation there were still no headaches. At eighteen months fleeting paralysis of the arm was noted, and at twenty months a stroke occurred. At twenty-four and twenty-nine months residual paralysis was obvious. At forty months a major vascular occlusion occurred in the region of the external capsule of the brain on the left, leading to dysarthria and marked mental deterioration. During this entire postoperative period, however, there was no marked change in the retinal findings, in the renal function or in blood pressure, although at the end of forty months the fifteen minute phenolsulfonphthalein test showed diminishing renal function (fig. 1).

Summary of Case.—A 39 year old woman suffered from severe benign nephrosclerosis (no retinal exudates and hemorrhages). She was treated by bilateral implantation of pedicled muscle flaps into the scarified kidney. Her postoperative course indicates a progressive development of hypertensive encephalopathy, without significant deterioration or improvement of renal function.

Case 2.—F. P., a 29 year old man, was referred by Dr. Harold Lueth to the Research and Educational Hospital of the University of Illinois from the Evanston Hospital, which he had entered because of palpitation, precordial soreness, dizziness and poor vision. In 1925 the patient was first discovered to have hypertension. Although he had been bothered for the past eight years with poor vision and nycturia, he had felt well until six and one-half weeks before entrance to the hospital, at which time he had a severe spell of dizziness, headache and nausea. He stated that he had had a severe headache ever since. He could not read a newspaper with his left eye. At the age of 8 he had scarlet fever, which was not known to have been followed by nephritis. His father died of apoplexy; his mother had high blood pressure. Examination of the ocular fundi showed papilledema of 2 D. on both sides, tortuous spastic vessels with perivascular infiltrations and recent and old hemorrhages. The heart was enlarged to the left; the aortic arch was dilated. The urine contained from 2 to 6 Gm. of albumin daily. The concentration-dilution test showed the specific gravity of the urine to range from 1.020 to 1.015; the urea clearance was 12.05 cc. per minute, and the urea ratio was 51. The rate of phenolsulfonphthalein excretion was 19 per cent at forty-five minutes and 40 per cent at one hour and forty-five minutes. The blood pressure varied from 230 to 206 mm. of mercury systolic and from 156 to 136 mm. diastolic. Nine grains (0.58 Gm.) of sodium amytal did not lower his blood pressure, which also failed to respond to potassium sulfocyanate. The electrocardiogram showed marked myocardial impairment. On Feb. 2, 1939 a typical nephro-omentopexy was done by bringing out a flap of omentum through the peritoneum and wrapping it around the decapsulated

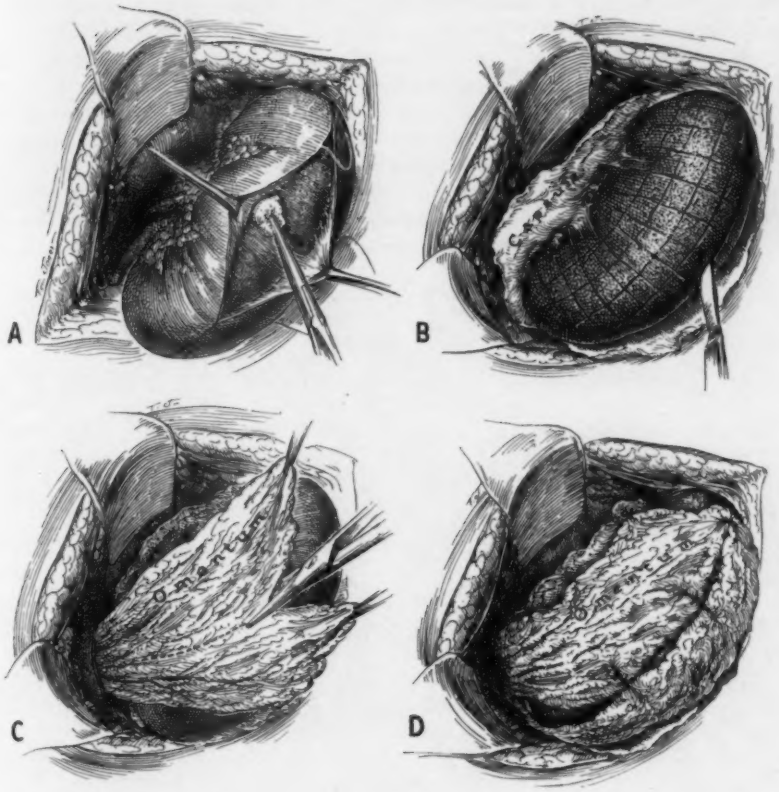

Fig. 2.—*A*, the kidney is exposed in the usual manner; in some cases a high muscle-splitting incision of the anterior abdominal muscles is done as for lumbar sympathectomy, so that a large lateral peritoneal surface is available. The kidney is delivered into the wound, and a longitudinal incision is made on its convexity. The capsule is grasped with Allis forceps and stripped of the cortex with a small moist pledget of cotton. *B*, after the capsule is reflected as far as the pedicle of the kidney, the cortex is scarified with the edge of the scalpel to prepare the kidney for the graft. A deeper incision is made on its convexity. The oozing must be stopped with hot saline compresses. *C*, a small incision is made in the peritoneum medial and caudal to the pedicle of the kidney; a flap of omentum is delivered and carefully split in the middle. The omentum is anchored to the peritoneal slit with a few interrupted sutures. *D*, the scarified kidney is wrapped in omentum which covers both the anterior and the posterior surface. A few interrupted sutures anchor the omental flaps to the reflected capsule and to each other. Enough space should be left to allow for drainage of any blood accumulating between the omentum and the kidney. A large hematoma, when organized, may readily form a heavy scar around the kidney and completely defeat the purpose of the operation.

and scarified right kidney (fig. 2). The kidney seemed small and firm, with whitish scars on the surface. A biopsy specimen taken from its cortex showed arteriolar sclerosis, with mostly intact glomeruli (fig. 3).[11]

The postoperative course was uneventful. Five months after the operation the patient was readmitted for a postoperative study. He complained of marked dizziness and a discharge from the right ear, which had been intermittently present ever since he had had scarlet fever at the age of 8. The blood pressure was 276 systolic and 184 diastolic. Potassium sulfocyanate, 3 grains (0.19 Gm.) three times a day, was given but could not be tolerated. Ten per cent dextrose had to be given intravenously for several days; in five days he could again take food by mouth. His dizziness improved, but only if he stayed in the horizontal position. His heart

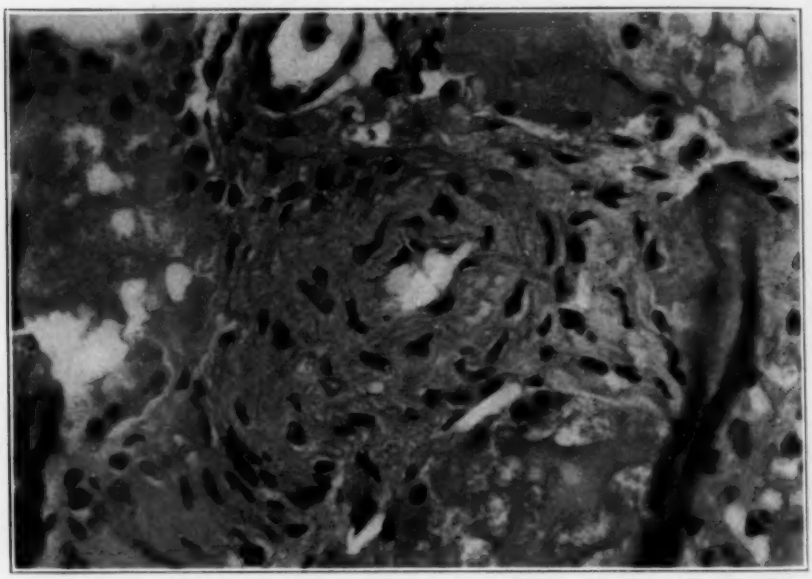

Fig. 3 (case 2).—Renal biopsy specimen from F. P. Generally speaking, the glomeruli are fairly well preserved. About 15 per cent of them, however, show varying changes, beginning with obliteration of the capillary loop boundaries, swelling of the epithelium with proliferation of the cells and swelling of the endothelium. Occasionally synechiae are demonstrable between a portion of the glomerulus with the Bowman's capsule. A few of the glomeruli are shrunken and even obliterated, with secondary hyalinization. Some of Bowman's capsules are markedly thickened by dense fibrous tissue. Such glomeruli are accompanied by thickening of the afferent and efferent arterioles as a result of fibrous tissue proliferation and hyalinization. Not infrequently the lumens are not discernible, or hyalin may replace the entire structure. The walls of the interlobular arteries are thickened and show similar changes.

The convoluted tubules seem to be reduced in number; the nuclei of the lining epithelium are pyknotic. The interstitial tissues show moderate fibrosis. The capsule of the kidney is thickened and shows regular depressions. Adjoining the latter areas the collecting tubules are dilated. There is no evidence of arteriolar necrosis anywhere. Note the marked arteriosclerosis in the center of the field.

11. The study of renal biopsy specimens was made by Dr. Sol R. Rosenthal.

became enlarged to the left. Bilateral choked disks were present. The acute edema of the brain was finally relieved. On July 23 he could be up and about without dizziness or headaches. His blood pressure fell to 230 systolic and 160 diastolic. The urea clearance was 33.2 cc. per minute, and the urea ratio was 57, showing an improvement in urea clearance but a deterioration of the urea ratio. The daily excretion of protein dropped from 14 Gm. at the second admission to 5 Gm. at discharge.

A third admission was made to the Evanston Hospital seven months after the operation. The patient had had several attacks of cerebral edema meanwhile and had suffered from severe headaches, nausea and vomiting. Between these attacks he was fairly comfortable. On entrance the heart was enlarged to the midaxillary line; there was moderate edema of the legs and ankles, and the face was puffy. The blood pressure ranged from 250 to 220 systolic and from 170 to 160 diastolic. The edge of the liver was palpated at the level of the umbilicus. Ophthalmoscopic examination showed three fresh hemorrhagic areas in the left fundus. The specific gravity of the urine was fixed at 1.010. A phenolsulfonphthalein excretion of 7 per cent could be obtained at ninety-five minutes. The urea clearance showed 2.9 cc. of blood cleared of urea per minute, 5.5 per cent of the average normal function. The electrocardiogram showed no change as compared with former tracings.

The patient was dehydrated with ammonium chloride and mercupurin (a mercurin-theophylline preparation) several times, which resulted in marked diuresis. The level of nonprotein nitrogen, however, varied from 70 to 100 mg. per hundred cubic centimeters; the value for urea nitrogen, from 48 to 56 mg. per hundred cubic centimeters and the urea ratio, from 69 to 75.[12]

Summary of Case.—A 29 year old man was subjected to unilateral nephro-omentopexy. At the time of operation he had obvious signs of fulminating malignant nephrosclerosis. Section of the splanchnic nerve in such a patient has never been of any benefit. The omental graft similarly failed to make an impression on the course of the disease. Death from uremia occurred ten months after the nephro-omentopexy.

Case 3.—Shirley S., a 7 year old girl,[13] was referred to the Research and Educational Hospital by Dr. Woodruff L. Crawford of Rockford, Ill. She was admitted on March 1, 1937, with a history of vomiting spells, headaches and convulsions. Choked disks and high blood pressure were discovered by Dr. Crawford, who sent the patient for observation and possible treatment. Symptoms had been present for about two years.

The girl was pale and undernourished. She showed marked cutis marmorata. Both papillae showed edema of between 5 and 6 D. The heart was enlarged to the left; the aortic and pulmonic second sounds were accentuated, without murmurs. There were no palpable masses in the abdomen. The reflexes were normal. Dr. Eric Oldberg found nothing to suggest a brain tumor. The blood count and the

12. On November 26, approximately ten months after the operation, the patient died at the Evanston Hospital. At autopsy the flap of omentum was seen firmly attached to the lower pole of the right kidney. Vessels were well visible coursing through the flap. The fat had completely disappeared. Sections taken from this kidney and the left one showed no changes compared with the section obtained through the biopsy specimen. The heart was markedly enlarged to the left; death resulted from terminal uremia.

13. This patient was in the pediatric service of Drs. Hess and Poncher, who gave permission for perusal of the history.

urine were normal. The blood pressure fluctuated from 290 to 230 mm. of mercury systolic and 190 to 160 mm. diastolic. A daily blood pressure curve was charted for several months but was lost between departments. The fluctuations of blood pressure were so marked that pheochromocytoma of the adrenal or of the paraganglions was suspected. A retrograde pyelogram revealed that the right kidney was larger than the left, and questionable clubbing of some of the calices on the left side was reported. A concentration-dilution test of the urine showed a specific gravity between 1.024 and 1.008. The phenolsulfonphthalein excretion was 50 per cent in one-half hour, 65 per cent in one hour and 80 per cent in two hours. The urea clearance was 31 per cent and 32 per cent. The values for nonprotein nitrogen were 36, 29, 27 and 39 mg. per hundred cubic centimeters. The value for urea nitrogen was 15 mg. per hundred cubic centimeters; the urea ratio was 51. Excretion of lead in the urine was within normal limits for this area.

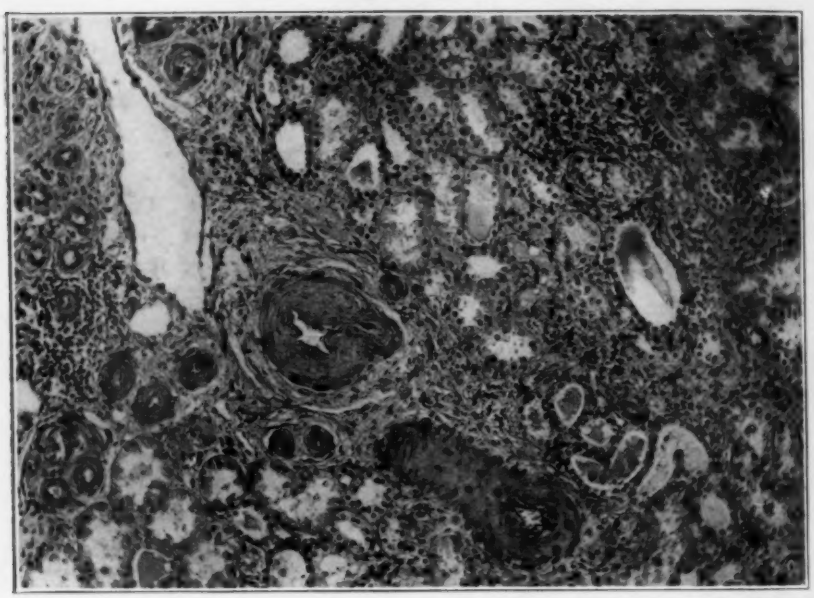

Fig. 4 (case 3).—Specimen from the right side (hypertrophic). The majority of the glomeruli seem well preserved; some of them show shrinking and fibrosis. The small and medium-sized arteries, where visible, show marked thickening of their walls, with almost complete obliteration. The intralobular arteries and the arcuate arteries show slight to no change. The tubules in the cortex show alternating areas of distention and collapse. In the latter areas the interstitial tissue is markedly increased. The capsule is depressed at regular intervals. At the site of depression the fibrous areas just described are observed. The pelvis presents a loss of epithelium with edema and fibrosis of the subepithelial tissues. Note the marked hyaline arteriosclerosis in the arterioles and small arteries.

The girl had severe hypertension papilledema and increased size of the heart and aorta. The total renal function was remarkably good, although the urea clearance rate and the urea ratio showed indications of impairment. The first operation was undertaken to explore the left adrenal region, as the hypertension

showed paroxysmal fluctuation varying as much as 100 mm. of systolic pressure. She had one severe attack of hypertensive encephalopathy, during which she almost died of acute cerebral edema.

On April 13, 1937 the left kidney and adrenal gland were explored. The left kidney was small and very firm and showed a granular surface; it revealed multiple areas of pitting and had the appearance of nephrosclerosis. A small wedge of renal tisse was taken for biopsy. The left adrenal gland seemed slightly enlarged, although the surgeon (G. de T.) was unable to be sure how large a 7 year old child's adrenal should be. It seemed firm and had the consistency of a rabbit's ear. In the retroperitoneal space there was a long chain of grayish hyperplastic lymph glands. A biopsy specimen was taken of these for identification. Closure of the wound was made with silk.

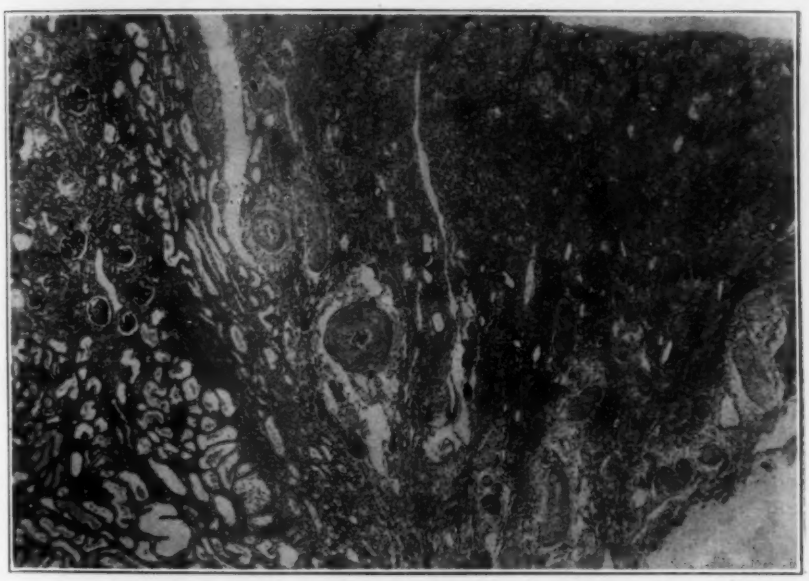

Fig. 5 (case 3).—Specimen from the left side (atrophic). The section of the kidney is divided into two distinct parts connected by dense fibrous tissue, proliferating tubules and thickened arteries. To one side of this junction the renal architecture is obscured, and there one notes hyalinized, thickened and obliterated vessels and perhaps glomeruli interspersed with small tubules with deeply staining nuclei and hyaline casts in the lumens. Round cells are numerous within the dense fibrous interstitial tissue. To the other side glomeruli are found, which are normal in appearance but in more instances are surrounded by fibrous tissue and atrophic tubules. The arterioles and small arteries in the main show no thickening. The intralobular arteries show slight to no thickening except for an occasional thickened vessel.

The tubules show areas of slight dilatation alternating with areas of compression fibrosis and even proliferation. The capsule is slightly thickened and depressed, corresponding to interstitial fibrosis.

The diagnosis was: right kidney, moderate arteriolosclerosis; left kidney, complete atrophy of one portion and slight arteriolosclerosis of the remaining portion.

The child stood the operation well. The renal biopsy revealed marked arteriolar obliteration, with preserved glomeruli and no stasis in the vascular tree. In the removed lymph glands the arteriolar changes were even more extensive.

On April 27, two weeks later, the right side was similarly explored. The right kidney was much larger and softer than the left. The right adrenal was smaller and more friable than the left. Because the presence of an adrenal tumor had been excluded, the right major, minor and minimal splanchnic nerves were identified under the diaphragm and were traced and sectioned at their entrance into the celiac ganglion. The right kidney was then decapsulated and scarified, and a piece of muscle with a broad pedicle was swung around the raw surface of the kidney. There was very little oozing. During this procedure the blood pressure fell to 90 mm. of mercury systolic and 80 mm. diastolic but was restored by two doses of neosynephrin hydrochloride. Closure was made in layers, with silk and without drainage.

The child's convalescence was uneventful, the wound healing by primary intention. The blood pressure, however, did not change, although it seemed more stable. The girl had several spells of cardiac asthma and became edematous. The liver became enlarged; the heart, especially the right side, was enlarged. She was given digitalis and was in an oxygen tent for three weeks before death, which occurred on June 7, six weeks after the second surgical procedure.

Autopsy revealed left ventricular hypertrophy, with moderate dilatation of all chambers of the heart; atelectasis of the lower lobe of the right lung; fatty changes in the liver; marked bilateral nephrosclerosis with atrophy of the left kidney, and edema of the brain with slight hydrocephalus.

The left kidney weighed only 37 Gm; the capsule was thick and stripped with difficulty, leaving a rough, reddish brown granular surface; the right kidney weighed 62 Gm., and a thick, well adherent mass surrounded the decapsulated kidney. Histologic sections of the two kidneys (figs. 4 and 5) showed no marked difference between the two sides. The glomerular tufts were filled with red cells. The convoluted tubules were in a severe stage of degeneration. The collecting tubules contained many hyaline casts. Some of the glomeruli were very cellular, and the capillary epithelium appeared slightly thicker than normal. The smaller vessels showed marked intimal proliferation, almost to occlusion of the lumen, and the medium-sized vessels showed intimal thickening and some thickening of the muscularis. The histologic diagnosis was nephrosclerosis, with complete atrophy of one part of the left kidney.

Summary of Case.—A 7 year old girl, suffering from a severe fluctuating type of hypertension, choked disks, convulsions and vomiting spells showed no adrenal tumor on exploration, but there was marked hypoplasia of one kidney, with compensatory hypertrophy of the other. Superimposed on the congenital anomaly was malignant nephrosclerosis. Cardiac compensation was maintained with difficulty. A unilateral decapsulation and application of a muscle flap did not arrest the disease, which ended in cardiac failure.

CASE 4.—Mrs. Rose B., 32 years old, had suffered from lupus erythematosus for eight years. She had received several treatments with sodium thiosulfate. Her blood pressure was 125 systolic and 74 diastolic in December 1935 and 138 systolic and 90 diastolic in June 1938. Her mother had diabetes and hypertension. In May 1934 the patient had eclampsia and miscarried in the sixth month of pregnancy. In 1935 she again had eclampsia when five and one-half months pregnant. The blood pressure then was 214 systolic and 140 diastolic. A cholecystectomy was performed in June 1934 and a salpingo-oophorectomy in 1938; neither of these operations affected the lupus. In July 1938 she suddenly experienced

numbness in both feet; this symptom gradually disappeared in two to three months, but cramping of the calves remained; at the time of admission she could hardly walk half a block. There were also some tingling and itching of the hands; occasionally red splotches would appear, which would disappear in two or three days.

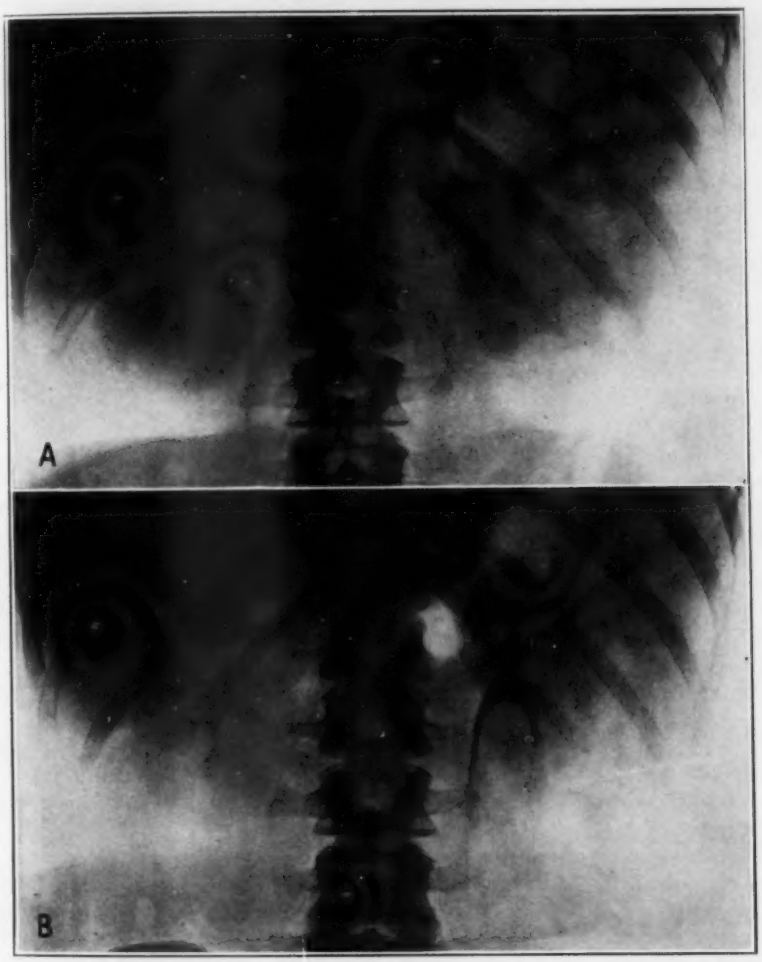

Fig. 6.—*A*, intravenous pyelogram of Mrs. R. B. taken ten minutes after injection of diodrast. The right renal pelvis (at left of photograph) is well filled with the dye and shows normal contours. There is no trace of dye on the left side. *B*, intravenous pyelogram taken forty-five minutes after injection of diodrast. The right renal pelvis (at left of photograph) is almost empty. The left pelvis has just filled; it was invisible at thirty minutes.

On her entrance to St. Luke's Hospital, March 6, 1939, butterfly areas of lupus erythematosus were found on the cheeks and faded spots on the arms and upper part of the chest. The pulses were impalpable on the lower extremities,

including both femoral pulses at the groin. The radial arteries pulsated well. The blood pressure was 170 systolic and 120 diastolic. It did not fall on administration of nitrites or of pentobarbital sodium. The oscillometric index at the left ankle was 0.5 cm. at 80 mm. of mercury and was the same at the right ankle. The upper part of the left arm showed an oscillometric index of 3 cm. at 120 mm. of mercury on the left and 3 cm. at 140 mm. on the right. The urine was normal; the urea clearance was 29 cc. of blood per minute, and the urea ratio was 38. The eyegrounds were normal. An intravenous pyelogram showed the dye in five minutes in the right kidney but not before the end of forty-five minutes on the left side (fig. 6). Cystoscopic study and ureteral catheterization (Dr. W. J. Baker) revealed that the urine from the right ureteral orifice was deep amber and that from the left pale and watery. The intravenous phenolsulfonphthalein appeared on the right side in four and one-half minutes, with excellent concentration, but none had appeared from the left side in fifteen minutes. Dr. E. H. Oliver thought that the lupus was quiescent and that previous surgical operations had caused no flare-up of the condition.

The history of eclampsia, the prolonged treatment with a gold compound and the presence of lupus erythematosus suggested a vascular lesion in the kidney; in addition, the occlusion in both iliac arteries and possibly the aorta suggested a Goldblatt kidney. The diagnosis of endocarditis as described by Libman in connection with lupus erythematosus could not be made. The possibility of periarteritis nodosa was suggested by Dr. R. W. Keeton.[14]

Operation (on March 11) was undertaken with the idea of exploring or possibly revascularizing the left kidney and at the same time sectioning the lumbar sympathetic nerves to improve circulation to the left lower extremity. The aorta, exposed by an anterolateral muscle-splitting incision, was small and collapsed and did not pulsate at the level of the umbilicus. The lumbar portion of the sympathetic chain was removed on the left between the first and the third lumbar ganglion. The left kidney was exposed. It was of normal color but definitely small, with small cortical scars and fatty deposits. A section removed from its middle third hardly bled (fig. 7). The pedicle pulsated, but more feebly than on the other side. Distal to the aorticorenal junction the aorta was pulseless; proximal to it there was strong pulsation. The kidney seemed like a Goldblatt kidney, but because of the lupus and its possible effect on the other kidney the thought of a nephrectomy was abandoned. The left kidney was decapsulated, scarified and wrapped in a pedicled flap taken from the psoas muscle. Closure was made with an all-silk technic, without drainage.

The patient stood the operation well; her blood pressure remained elevated and stable throughout the operation. However, on the third day a rise in temperature occurred, together with gallop rhythm, some pulmonary congestion and edema of the ankles. Dr. R. W. Keeton ordered administration of digitalis and restriction of fluids; under this management the gallop rhythm subsided, and the process in the left lung did not progress. On the fifth postoperative day the patient seemed definitely better and was taking foods and fluids by mouth. However, at the end of the fifth day there occurred a sudden severe pain high over the dorsal part of the spine and the chest, and the gallop rhythm returned. The temperature rose to 102. A portable x-ray apparatus showed a questionable shadow behind the heart, in the posterior mediastinum (Dr. E. L. Jenkinson), but an oblique view could not be obtained with the portable apparatus. The patient became toxic and delirious and

14. In a recent case of lupus erythematosus, Dr. Tracy B. Mallory made the pathologic diagnosis of periarteritis nodosa (Cabot Case 24201), New England J. Med. **218**:838 [May 19] 1938).

expectorated dark, frothy mucus in large quantities; gradually cyanosis set in, which did not improve with digitalis and oxygen therapy. On the sixth day difficulty in swallowing occurred. The toxicity increased, and the patient died, seemingly from pulmonary edema, on the sixth postoperative day. Permission for autopsy could not be obtained. As a cause of death, reactivation of the lupus erythematosus was suggested by the high temperatures, the marked toxicity, an unexplainable septicemia with sterile blood cultures and the absence of reaction in the wound. But the questionable shadow in the mediastinum, the pain in the chest, the difficulty in swallowing and the cardiac insufficiency made one wonder whether ascending aortic thrombosis was not present.

Summary of Case.—A 32 year old woman suffering from lupus erythematosus, unilateral renal disease, hypertension and vascular occlusion of the aorta was subjected to an exploratory procedure and lumbar sympathectomy, and a left renal vascularization was performed. She died six days after the operation. The cause of death was not determined. Biopsy revealed nephritis, which is not infrequently associated with lupus erythematosus.

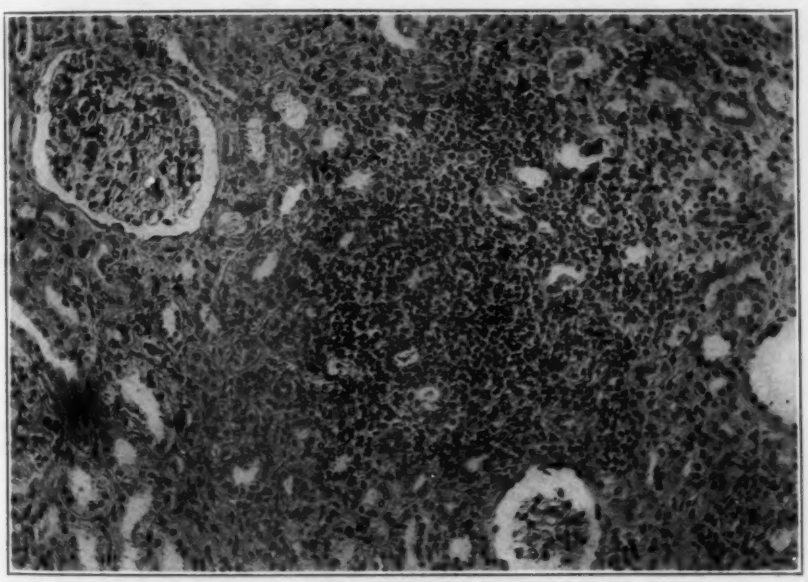

Fig. 7.—Photomicrograph (Mrs. R. B.). The glomeruli show no abnormal changes except for thickening of Bowman's capsule. The arterioles and arteries show slight to no thickening. The most striking changes are in the interstitial tissues. There are focal areas of infiltration of large lymphocytes and plasma cells. There seems also to be an increase in the interstitial fibrous tissue. In some areas compression and obliteration of the convoluted tubule can be seen.

The impression was that of interstitial lymphoblastic plasmocellular nephritis with fibrosis. There was moderate arteriolar obliteration.

COMMENT

The 4 cases presented differ greatly, and it may be well to deal with them individually. The first case is perhaps the most instructive, because

follow-up records are now available since April 1936. The condition had to be classified as benign nephrosclerosis because of the absence of retinal hemorrhages and exudates, but definite impairment of renal function was present. The urea clearance and urea ratio have not changed appreciably for four years. Nor has the heart shown any deterioration, as checked by physical findings and electrocardiograms. The vascular encephalopathy, which manifested itself as the earliest symptom in fleeting paralysis of the arm, progressed to hyperactive reflexes, headaches, papilledema and blurred vision, and, after repeated strokes, mental deterioration is now in its terminal stage and will most likely be the cause of death. That such cerebral episodes are not dependent on renal function was first convincingly demonstrated by the work of Volhard.[15] Neither the tests of renal function nor the nitrogen retention showed any deterioration of renal function while the cerebrovascular episodes repeated themselves. The statistics of Christian[16] show that, of 131 patients who died of hypertension in the hospital, 32 per cent died of cardiac failure, 25 per cent of cerebral accidents, 25 per cent of conditions independent of hypertension and only 4.5 per cent of uremia or with severe renal disease. Similarly, Bell and Clawson[17] found that of 420 patients who died of essential hypertension, 49.3 per cent died of cardiac failure, 19 per cent of cerebral apoplexy or thrombosis, 15 per cent of coronary disease, 10 per cent of accidents or intercurrent disease and 8.6 per cent of renal disease. The cause of death from renal failure is thus the least frequent of all causes of death from essential hypertension, and it would seem that, once the arterial hypertension has persisted for a time, vascular damage in different organs and failure of the heart will be the causes of death. Less than 10 per cent of the patients survive long enough for renal failure to occur.

Therefore we do not feel that the process in the case of Alma J. has been influenced, even though renal impairment has not progressed since the operation.

Even more clear is the progress of nonrenal vascular damage in the case of F. P. (case 2). The malignant nephrosclerosis in this patient, a 29 year old man, obviously carried the worst possible prognosis. The medical department felt that in such a hopeless case any surgical procedure is justified. But the surgeon may just as well accept a patient with inoperable carcinoma in the terminal stage as try to save a patient

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15. Volhard, F., in Mohr, L., and Staehelin, R.: Handbuch der inneren Medizin, Berlin, Julius Springer, 1918, vol. 3, pp. 139-168.

16. Christian, H. A., in discussion on Andrews, C. L.: Circulatory Tonics Versus Circulatory Depressants in Cardiovascular Renal Disease with Hypertension, J. A. M. A. **87**:928 (Sept. 18) 1926; in discussion on Paullin, J. E.: Ultimate Results of Essential Hypertension, ibid. **87**:925 (Sept. 18) 1926.

17. Bell, E. T., and Clawson, B. J.: Primary (Essential) Hypertension: Study of Four Hundred and Twenty Cases, Arch. Path. **5**:939 (June) 1928.

with a diffuse arteriolar lesion in many organs. This patient died ten months after the operation, with gradual failure of his cardiovascular and renal systems.

The third case, that of a 7 year old child, varies from the first 2 in causation of the condition. The type of juvenile malignant nephrosclerosis in conjunction with congenital hypoplasia of one kidney observed in this case has been discussed by Ask-Upmark,[18] who published 6 cases in which autopsy was performed. The anomalies consisted of unilateral hypoplasia, absence of cortical tissue with development of blind subcapsular diverticula communicating with the pelvis of the kidney and, finally, cystic spaces filled with colloid material. Normal kidney tissue alternated with normal renal parenchyma. We have observed 1 case besides the one described; this was the case of an 8 year old girl suffering from malignant nephrosclerosis, in whom perirenal insufflation revealed marked hypoplasia of one kidney; she was seen at a terminal stage of cardiac failure, and operation was not considered.

If pediatricians were uniformly in the habit of recording blood pressures, juvenile malignant hypertension might be recognized earlier. The removal of a hypoplastic kidney before the other kidney has suffered vascular damage seems logical, since unilateral pyelonephritic kidneys causing hypertension have been successfully removed by Butler,[19] Barney and Suby [20] and Barker and Walters.[21] But it must be stated that removal of one ischemic kidney producing a pressor substance may occur at a time when the other kidney has become involved. Thus, in the case of Shirley S. the histologic picture of the large compensatory kidney could not be distinguished from that of the hypoplastic one; it is even possible that such an enlarged kidney is more vulnerable, as Leiter [22] has suggested. If nephrectomies are to be carried out because of unilateral ischemic kidneys, involvement of the other kidney will have to be carefully scrutinized; it may elude the most sensitive tests of renal function at the time. In the case of Shirley S., nephrectomy of the atrophic kidney might have been curative within the first few months after the onset of symptoms, two years before admission to the hospital.

In the fourth case there were so many unusual features that the diagnosis eluded several diagnostic clinics. On admission it became apparent

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18. Ask-Upmark, E.: Ueber juvenile maligne Nephrosklerose und ihr Verhältnis zu Störungen in der Nierenentwicklung, Acta path. et microbiol. Scandinav. **6**:383, 1929.

19. Butler, A. M.: Chronic Pyelonephritis and Arterial Hypertension, J. Clin. Investigation **16**:889, 1937.

20. Barney, J. D., and Suby, H. I.: Unilateral Renal Disease with Arterial Hypertension, New England J. Med. **220**:774, 1939.

21. Barker, N. W., and Walters, W.: Hypertension in Unilateral Renal Disease, Proc. Staff Meet., Mayo Clin. **15**:475, 1940.

22. Leiter, L.: Personal communication to the authors.

that there existed (1) quiescent lupus erythematosus, (2) unilateral renal disease with poor excretory function and (3) a major vascular occlusion involving the aorta, at least, at the iliac bifurcation. The combination of lupus erythematosus and renal disease has been well described by Snapper [23] and by Baehr, Klemperer and Schifrin; [24] the occurrence of endocarditis with lupus has been emphasized by Libman and Sachs,[25] but in this case we suspected a unilateral Goldblatt kidney, which would explain both the renal damage and the pulseless extremities by occlusion of the aorta at the level of the left renal artery. This proved to be the case at operation. In retrospect, a nephrectomy might have been better than the muscle transplant; section of the splanchnic nerve, considered elsewhere, did not seem indicated. Whether death occurred because of a toxemic manifestation of lupus erythematosus or because of a propagating thrombus of the aorta is open to question.

The conditions described in these 4 cases are examples of desperate terminal hypertension. Instead of approaching the surgical treatment of these conditions by section of the splanchnic nerve, the results of which we now have observed up to six years, an attempt was made to graft new circulation on these ischemic kidneys. We cannot say that in the 1 surviving patient the course of the disease has been altered. Our experience, however, serves to emphasize that renal failure is not frequently the cause of death of patients suffering from essential hypertension and that an intravenous pyelogram readily shows differences in size and function of the two kidneys and might demonstrate unilateral renal involvement in the early stages. Nephrectomy at that time, as is shown by cases in the literature, may be curative.

But the majority of patients with essential hypertension show arteriolosclerosis of both kidneys; [26] we have learned this by renal biopsies in the cases of young patients who showed no signs of organic damage and had flexible, moderate hypertension (fig. 8). We shall report on a group of patients subjected to splanchnic nerve section in another communication.

Perhaps this surgical exploration of the kidneys of hypertensive patients needs some apology. Certainly no other measure has come to our attention that would alter or arrest the course of hypertension.

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23. Snapper, I.: Kidney Trouble in Acute Lupus Erythematosus, in Berglund, H., and Mides, S.: The Kidney in Health and Disease, Philadelphia, Lea & Febiger, 1935, chap. 26, pp. 433-439.

24. Baehr, G.; Klemperer, P., and Schifrin, A.: A Diffuse Disease of the Peripheral Circulation Usually Associated with Lupus Erythematosus and Endocarditis, Tr. A. Am. Physicians **50**:135, 1935.

25. Libman, E., and Sachs, B.: A Hitherto Undescribed Form of Valvular and Mural Endocarditis, Tr. A. Am. Physicians **38**:46, 1923.

26. Moritz, A. R., and Oldt, M. R.: Arteriolar Sclerosis in Hypertensive and Nonhypertensive Individuals, Am. J. Path. **13**:679, 1937.

If one looks at this disease as a malignant process—and, to be sure, cases of stationary, benign or regressive hypertension in patients below the age of 40 are not frequent—one must attack it with all available means, and not in the terminal stages. More use will have to be made of intravenous pyelograms for hypertensive patients, as they serve for an orientation of the size and function of the two kidneys; later, if the results of this preliminary test suggest it, differential tests of renal function can be carried out. Perirenal insufflation, which we have used in a number of cases to investigate the size of the adrenal glands, is fraught with danger to hypertensive patients, who often have a well developed

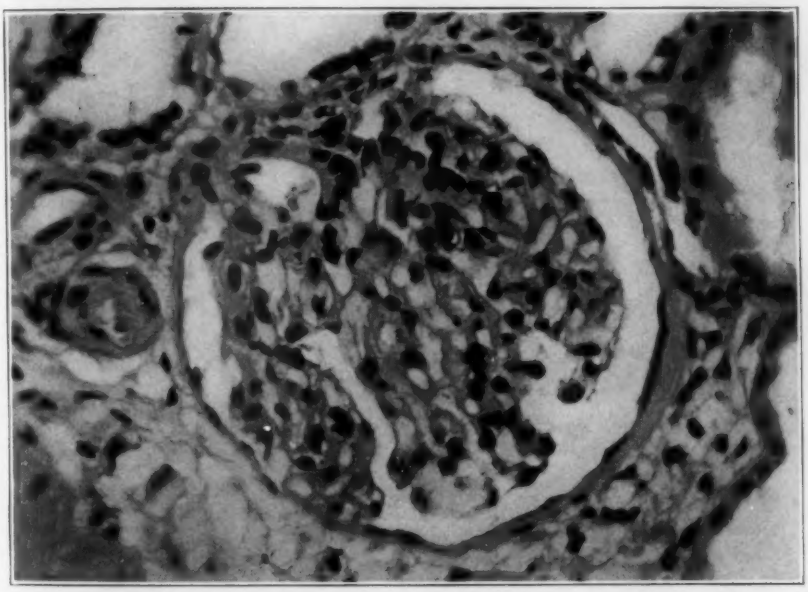

Fig. 8.—Renal biopsy specimen from M. S., a 24 year old woman in whose case a clinical diagnosis of latent glomerulonephritis was made. The capillary buds are distinct; the epithelium and endothelium show no swelling; the basement membranes do not appear to be thickened, and there is no fibrin deposit.

The afferent and efferent arterioles have rather thin walls and show a small amount of endothelial swelling. The interlobular and arcuate arterioles and small arteries show uniform thickening of this wall, varying in degree and in some instances practically occluding the lumen (diameter of one red cell). The wall is four or five times as thick as the diameter of the red cell.

The convoluted tubules are somewhat disrupted by artefacts, but their nuclei appear normal.

The diagnosis was: arteriosclerosis and arteriolosclerosis of the kidney. Note the intact glomerulus and the almost obliterated arteriole to the left.

collateral circulation in the perirenal fat. In the case of Edith H. (not reported here), a 29 year old unmarried woman in whose case the diagnosis of malignant nephrosclerosis was made, the right kidney was

outlined without difficulty, but not enough air was visible on the left side (fig. 9). After the perirenal injection on the left side, she had a severe reaction, which was due to a large perirenal hematoma; there was a huge amount of clotted and unclotted blood around the kidney and under the capsule, as was demonstrated later on exploration.

The results in our cases do not answer the question whether renal revascularization is of any value for patients suffering from nephrosclerosis; nor is it positively known that certain patients with chronic glomerulonephritis or pyelonephritis, who may undoubtedly have endarteritis obliterans in the afferent and glomerular vessels, would not be

Fig. 9.—Perirenal insufflation of 250 cc. of air in the case of E. H.: Only the right side was visualized. The film was taken twenty-five hours after injection. Note the triangular shadow above the upper pole of the kidney, representing a normal-sized right adrenal gland.

equally suitable for such a procedure. A combination of renal sympathectomy with decapsulation has recently been advocated by Chabanier and his associates.[27] These authors correctly pointed out that hypertension with nephritic symptoms may be due to malignant nephrosclerosis with glomerular manifestations or to chronic diffuse glomerular

27. Chabanier, H.; Gaume, P., and Lobo-Onell, C.: Vue d'ensemble sur les résultats d'interventions pratiquées dans quarante-neuf cas de néphroangiosclérose, Presse méd. **46**:1818, 1938.

nephritis with secondary vascular changes.* The result in both instances is the ischemic kidney; when unilateral, it can be removed, but this certainly does not apply to the majority of diffuse renal diseases. The greatest stumbling block to effective vascularization of an arteriolosclerotic kidney is that the vascular obstruction is terminal; this type of arteriolar destruction is the most difficult to treat in the extremities. Nevertheless, an extraglomerular circulation, affecting perhaps the tubules,[5] might still be of some use.[27a] We have put these cases on record to report the futility of this procedure in the late stages. We believe that revascularization should not be abandoned until it is evaluated by trial on patients with early benign nephrosclerosis giving the typical clinical picture of essential hypertension.

Finally, attention should be called to the frequent occurrence of partial obstruction of the main renal artery in association with "essential" hypertension in man. For kidneys with such obstruction which were studied as postmortem material by Blackman,[28] surgical procedures to increase the blood flow in the terminal vascular bed offer more promise.

SUMMARY

Four hypertensive patients in whose cases the diagnosis of malignant nephrosclerosis was made were operated on with the idea that the ischemic kidney might obtain some additional circulation. The kidneys were decapsulated; the cortex was incised and the omentum or a pedicled muscle flap was wrapped around the kidney. The 4 case reports are summarized. One patient has been followed for three and one-half years. In no patient was there a definite improvement. It is possible that if patients with essential hypertension with earlier or more proximal vascular damage were subjected to such a procedure the condition might be arrested or improved. The importance of taking renal biopsy specimens and the difficult interpretation of biopsy observations in the early stages are emphasized. For the late stages in which the patient is referred to the surgeon, renal vascularization has been of no value.

122 South Michigan Avenue.

27a. A study of the architecture of the kidney in chronic renal disease (Oliver, J.: Architecture of the Kidney in Chronic Bright's Disease, New York, Paul B. Hoeber, Inc., 1939) reveals the striking hypertrophy and hyperplasia of the proximal convoluted tubules in aglomerular nephrons, a phenomenon of repair.

28. Blackman, S. S., Jr.: Arteriosclerosis and Partial Obstruction of Main Renal Arteries in Association with "Essential" Hypertension in Man, Bull. Johns Hopkins Hosp. **65**:353, 1939.

SUTURE STUDIES

A NEW SUTURE

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A profound and exhaustive study of wound healing appears in an article by Arey,[1] which should be informative and illuminating to all students of surgery. This study was conducted without reference to the presence of sutures and stands virtually as a control for any study on wound healing complicated by additional influences. Thus a study of wound healing as influenced by sutures is of paramount importance from the standpoint of fundamental and practical application.

The controversy concerning absorbable and nonabsorbable sutures has been fluctuating ever since Halsted [2] broke away from the precedent of absorbable sutures to advocate the use of silk sutures.

In recent years the subject has interested me very much. In my experiences with various sutures, such as plain, chromic, tanned and iodized catgut and silk, linen, steel wire and artificial sutures, I have felt that the controversy concerning the relative merits of absorbable and nonabsorbable sutures is leading nowhere. I have become convinced that the emphasis in discussing sutures should be directed to whether a given suture is reacting or nonreacting.

From extensive clinical and experimental work I have tried to ascertain what factors exist in sutures in current use to make them react and have studied various sutures in the light of these factors.

I have enumerated five principal factors in the production of a reacting effect:

1. Absorbability of a suture.
2. Favorable bacterial medium from the split products of a suture.
3. Allergic sensitivity of tissues to foreign proteins in a suture.
4. Susceptibility of a suture to enzymatic digestion.
5. Capillary retention of stagnant serum within the body of a suture.

1. The more absorbable a suture is, the more soluble material there will be to diffuse out into the tissues and arouse an irritating response. In addition to this, the more soluble a suture is, the greater is the

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From the Surgical Service of the Collins Clinic.

1. Arey, L.: Wound Healing, Physiol. Rev. **16**:327-406, 1936.

2. Halsted, W. S.: Ligature and Suture Material, J. A. M. A. **60**:1119-1126 (April 12) 1913.

depreciation in certain of its physical properties, such as tensile strength and knot holding.[3]

2. The split products resulting from the breaking down of a suture of animal origin will offer an excellent culture medium for bacterial growth and will thus increase and extend the zone of injurious reaction. Inherent contamination of such a suture, which sometimes occurs with catgut, will yield an immediate pathogenic agent which will further aggravate this reaction.[4]

3. Allergic reaction from sensitivity of the tissues to the foreign proteins in the original suture or to its broken-down products has been observed too often to allow doubt of its injurious effect in delaying or impairing primary repair.[5]

4. A suture of animal origin or of protein composition lends itself in varying degrees to digestion by the trypsin-like enzymes ever present in the body tissues. The effect of this and of its aftermath gives rise to varying degrees of irritating response.[6]

5. The infiltration of serum or body fluids within the body of a suture by capillary attraction gives rise to stagnation of serum. This acts as a favorable culture medium for bacterial growth and leads to an inflammatory reaction within the suture and to extension of infection along the course of the suture.

The observation that any one or more of these factors inherent in a suture make that suture an inherently reacting one is a conclusion inevitably reached from a close study of suture reactions. Thus, catgut

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3. Howes, E. L., and Harvey, S. C.: Strength of Healing Wound in Relation to Holding Strength of Catgut Suture, New England J. Med. **200**:1285-1291, 1929. Jenkins, H. P.: Clinical Study of Catgut in Relation to Abdominal Wound Disruption, Surg., Gynec. & Obst. **64**:648-662, 1937. Rhoads, J. E.; Hottenstein, H. F., and Hudson, I. F.: Decline in Strength of Catgut After Exposure to Living Tissues, Arch. Surg. **34**:377-397 (March) 1937.

4. Meleney, F. L., and Chatfield, M.: How Can We Insure Sterility of Catgut? Surg., Gynec. & Obst. **50**:271-277, 1930. Clock, R. O.: Bacterial Species Found in Non-Sterile Surgical Catgut Sutures, ibid. **66**:878-881, 1938.

5. Babcock, W. W.: Catgut Allergy, with a Note on the Use of Alloy Steel Wire for Sutures and Ligatures, Am. J. Surg. **27**:67-70, 1935. Hinton, J. W.: Allergy as an Explanation of Dehiscence of Wound and Incisional Hernia, Arch. Surg. **33**:197-209 (Aug.) 1936. Kraissl, C. J.; Kesten, B. M., and Cimiotti, J. G.: Relation of Catgut Sensitivity to Wound Healing, Surg., Gynec. & Obst. **66**:628-635, 1938.

6. Allen, J. C. B.: The Fetish of Catgut, M. J. Australia **2**:150-151, 1934. Reil, H.: The Catgut Problem, Chirurg **4**:17-23, 1932. Kraissl, C. J., and Meleney, F. L.: A Method for Determining the Time of Catgut Digestion in Vitro, Surg., Gynec. & Obst. **59**:161, 1934.

reacts because of factors 1 to 4 inclusive. Natural silk reacts because of factors 4 and 5.[7] The treated silks, linen and rayon in current use react because of factor 5.

Hence all absorbable sutures and all reacting nonabsorbable sutures, by virtue of their irritating effect, would be expected to oppose primary physiologic repair.

It is an extremely significant observation that all the sutures in current use fall into the group of reacting foreign bodies. With a knowledge of this fact, it becomes readily comprehensible why dissatisfaction with these sutures has often been expressed.

There is a general conviction among physicians and surgeons alike that introduction of foreign bodies into the tissues inevitably gives rise to an unfavorable foreign body reaction, with the development of inflammatory cells, macrophages and giant cells and ultimately of a thick wall of fibrous tissue to wall off the foreign body.

It has been my observation that this contention is untrue and fraught with the liability of false conclusions. If the factor of pure mechanical irritation is eliminated, no one who has studied the behavior of foreign bodies, such as rustless steel wire, vitalium screws and glass, will deny that these foreign bodies are nonreacting within the tissues. Thus it is essential that in the consideration of sutures emphatic differentiation be made between reacting and nonreacting foreign bodies.

It was my endeavor to find a nonreacting foreign body which could be utilized as a suture that led me to the search for a nonreacting suture. In order to achieve the attainment of an ideal suture I postulated the requirements that seemed essential in such a suture. These are:

1. The suture should be sterilizable by common hospital and office methods, that is, by autoclaving and by boiling, without significant loss of desirable properties.

2. The suture should possess pliability, satisfactory tensile strength, knot-holding qualities and uniformity for given sizes.

3. The suture should be nonreacting or relatively nonreacting in the body tissues.

4. It should be insusceptible to the action of tryptic enzymes in the body tissues.

5. It should be insusceptible to the chemical and physiologic agents in the body tissues.

6. It should be unaffected by bacteria and incapable of promoting the growth of bacteria.

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7. Starlinger, F.: The Later Fate and the Clinical Effect of Silk Threads in the Wall of Gastro-Intestinal Fistulae, Zentralbl. f. Chir. **54**:2562-2566, 1937. Donaldson, J. K., and Cameron, R. R.: Study of Use of Silk, Catgut and the Noble Plication with Reference to Abdominal Adhesions, Surgery **5**:511-521, 1939.

7. It should be incapable of retarding the process of repair.

8. It should be incapable of inducing disturbing edema or of inducing effusion of tissue fluids in operative wounds.

9. It should be incapable of inducing allergic reaction and, incidentally, of inducing toxic or carcinogenic influences.

10. It should be practically unaffected by clinical ranges of heat and moisture.

11. It should be *truly* noncapillary.

12. It should permit ease in handling, at least equal to that of catgut.

13. It should be radiolucent.

The logical conclusion that arises from the foregoing requirements leads to the final requirement:

14. It should be nonabsorbable.

A study of present day sutures discloses the significant fact that none are available thus far that incorporate all of the properties just enumerated. The rustless steel alloy wire of Babcock and Kurlander [8] makes the closest approach. Its radiopacity and difficulty of surgical manipulability militate against its general use as a universal suture.

A type of suture which consists of silk wound around a core of steel wire has been described.[9] I have not used it but it may be assumed that it combines the disadvantages of silk and those of wire.

An attempt has been made to stain and adapt a new fiber called nylon [10] as a surgical suture. Little can be said as yet with regard to its utility. I have seen but one photomicrograph, which, taken at two days, was shown in contrast to a photomicrograph of an intense silk suture reaction at eight days but which itself showed a moderate inflammatory reaction at this early date. Moreover, monofilic nylon fails signally in one of the essential physical properties, that of knot holding, whereas the suture composed of multiple filaments may be expected to react much like the silk suture. However, it must be stated that the manufacturers have taken the precaution of recommending it only as a removable superficial suture.

The development of my new plastic suture is the result of a three year search for a nonreacting suture that attempts to combine all of the requirements enumerated. That objective has apparently now been attained, and after extensive experimental and personal clinical trial I have finally reached the point where I can, with confidence, introduce my improved suture, based on a new principle of nonreaction–plastigut.

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8. Babcock, W. W.: Ligatures and Sutures of Allow Steel Wire, J. A. M. A. **102**:1756 (May 26) 1934. Kurlander, J. J.: Rustless Steel Wire: A New Addition to the Surgeon's Armamentarium, J. Bone & Joint Surg. **12**:191, 1930.

9. Rau, O.: Experiences with the Modern Suture Material "Medrafil," Zentralbl. f. Chir. **64**:509, 1937.

10. Ziegler, P. F.: Du Pont Nylon Steps into Surgery, Du Pont Mag. **33**: 14-15, 1939.

Plastigut [11] is a nonreacting, nonabsorbable, noncapillary suture in which the essential components are synthetic plastics. These plastics are polymerized condensation products of aliphatic and aromatic alcohols with short chain aliphatic aldehydes. They may be considered analogous to bakelite, lucite and vinylite. The appearance of the suture is similar to that of catgut, and it is prepared in equivalent sizes, but from that point on the similarity ceases.

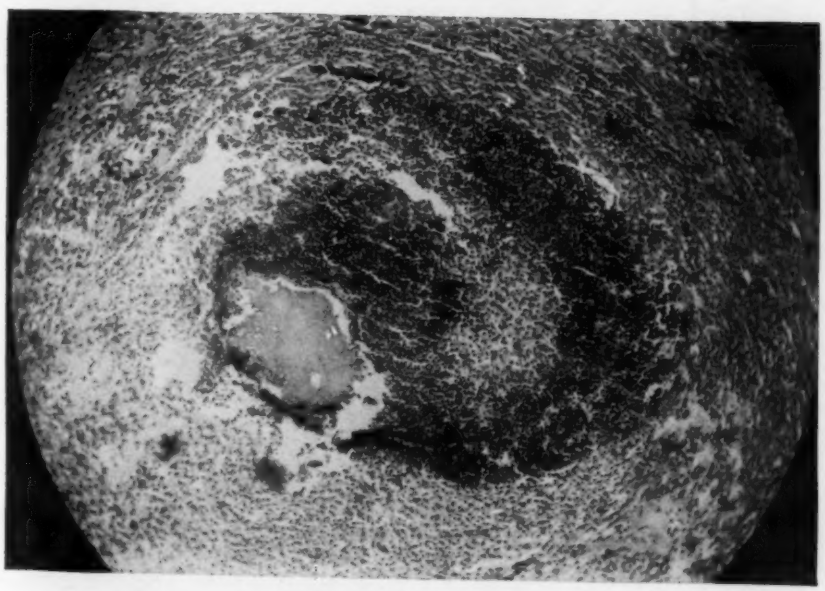
Animal experimentation was resorted to in order to study the effect of various sutures in relation to tissue reaction and to the process of wound healing as ascertained by microscopic studies. Plain and chromic catgut, natural and treated silks, natural and Pagenstecher linen and plastigut were embedded deeply in the tissues of guinea pigs and dogs, and at intervals between two days and six months the animals were killed and sections made of the various sutures. All the aforementioned sutures were buried in the same animal for many of the specified periods so as to have identical conditions. A large number of microscopic sections were thus obtained, of which the accompanying photomicrographs demonstrate the typical results.

To the practical surgeon, clinical trial is the most crucial test, and my own interest and curiosity led me to use plastigut in a few operative cases. The prompt healing and absence of reaction, as well as a definite reduction in the amount of pain from the incision in "clean cases" so gratified me that I was encouraged to use plastigut in an ever increasing percentage of cases until I found myself using it as the routine suture. My subsequent experience has only convinced me further of the value and range of utility of the suture. Another factor of economic importance is the shortened period of hospitalization which results from its use. It was obvious that the stage of repair in cases in which plastigut was used was far more advanced at any given day than in cases in which catgut was used, because there was no irritating inflammatory and exudative reaction to prevent or hinder repair. Subsequent postoperative incisional hernias suddenly became a rarity. Even vesicovaginal fistulas, which had formerly been a specter and a nightmare because of repeated recurrences, miraculously healed as by primary intention. It became increasingly apparent to me that when catgut was used the incisions eventually healed not because of but in spite of the catgut.

I have used plastigut in about 600 cases, but sufficient time has elapsed to give the ultimate results in only 406 cases. These represent an experience over a three year period in all types of cases, under all manner of conditions and with varied technics. I have learned a great many things about sutures in carrying out this work, particularly in relation to the use of plastigut. At first my sutures were crude and

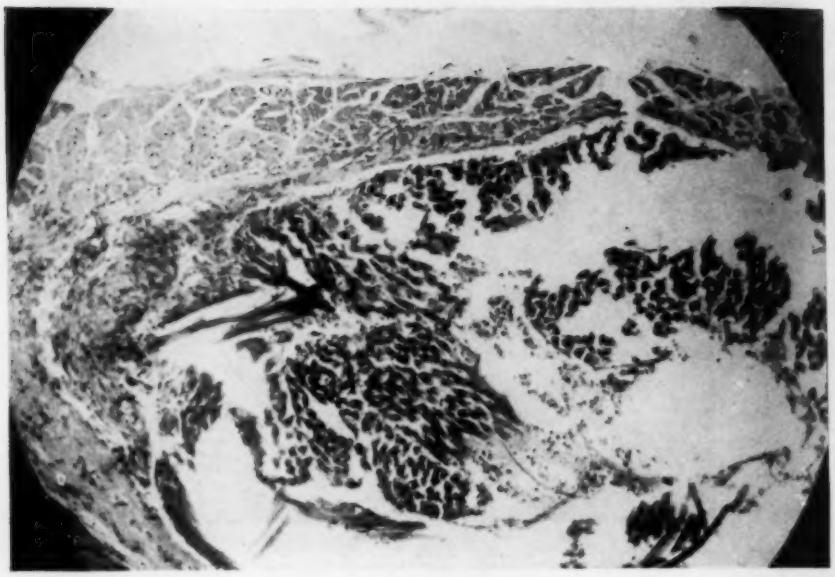
11. This name has been adopted for convenience and simplicity.

A

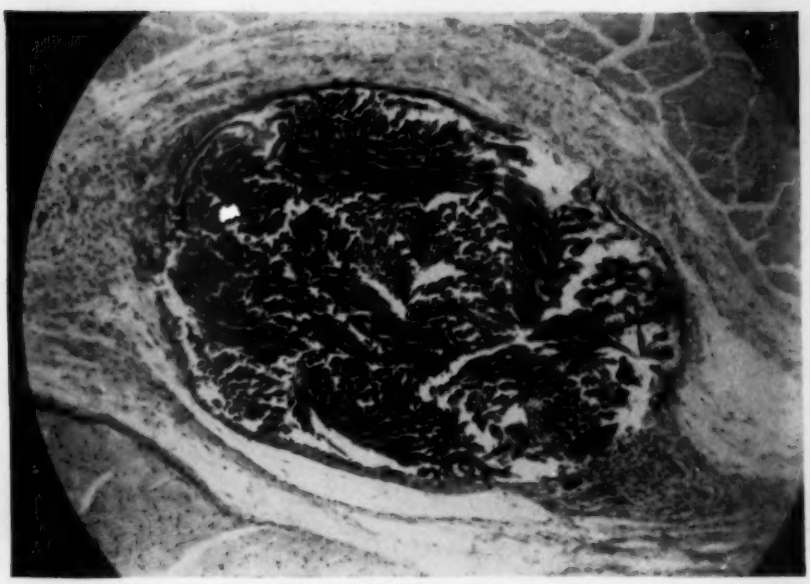


B

Fig. 1.—*A*, chromic catgut suture at the end of five days. The catgut suture is beginning to be absorbed. An inflammatory reaction is present, especially at the site of absorption. *B*, section at two weeks, in which a plain catgut suture is almost completely digested and replaced by a wide, rounded area filled with acute inflammatory cells and showing central necrosis. This is virtually an acute abscess. The photomicrographs are typical of the reactions with catgut.

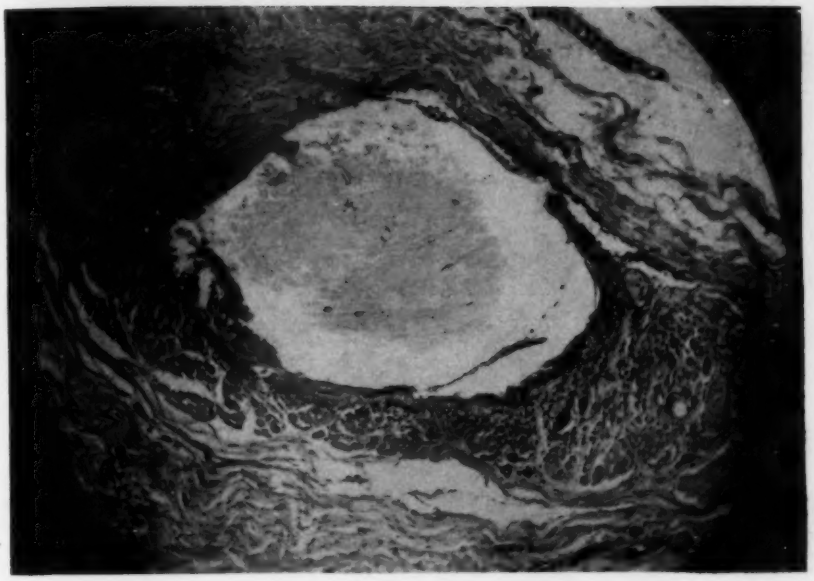


A

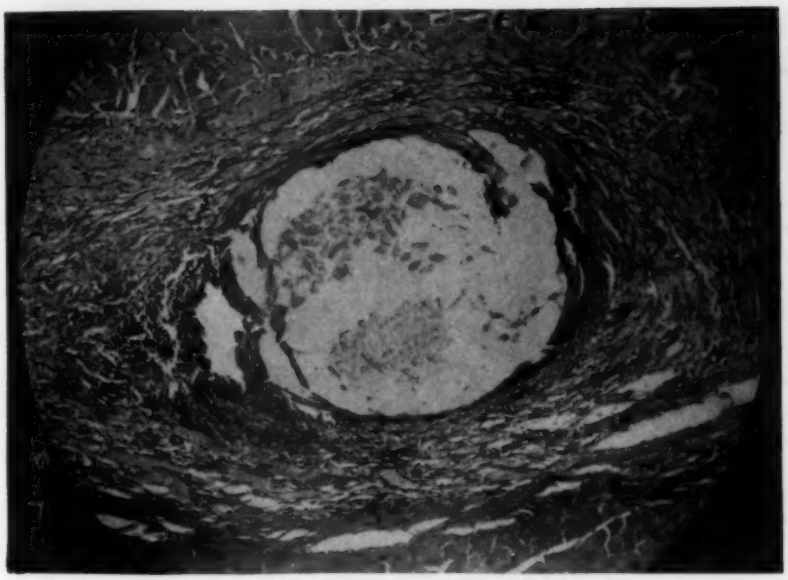


B

Fig. 2.—*A*, typical section of a silk suture claiming to be noncapillary and serum proof. At seven days a marked infiltration of inflammatory cells and serum can be seen between the fibers of silk. This shows definitely how capillarity favors the retention and promotion of infection. *B*, section at four weeks of another type of silk suture claiming to be serum proof and noncapillary. Note the presence of inflammatory cells within the structure of the suture and between the fibers.

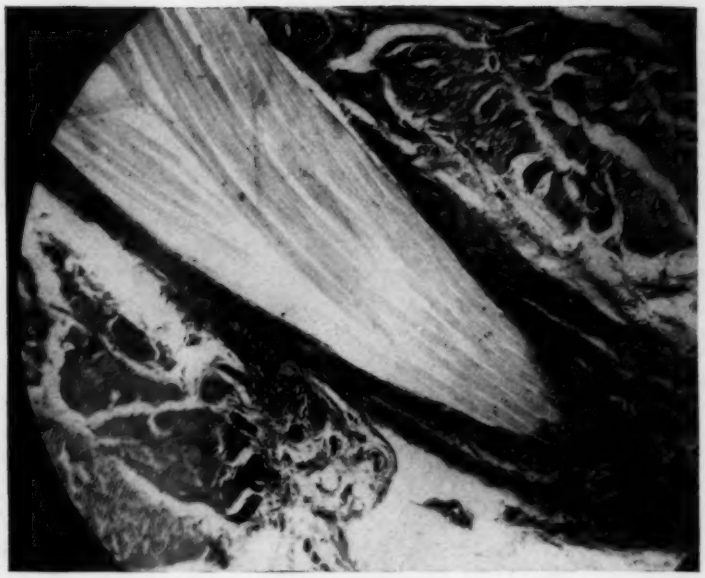


A



B

Fig. 3.—*A*, section of plastigut at seven days, showing the suture surrounded by normal tissue, with no evidence of inflammation in or around the suture. *B*, section of plastigut at two weeks. There is no reaction, no inflammation and no capillarity.



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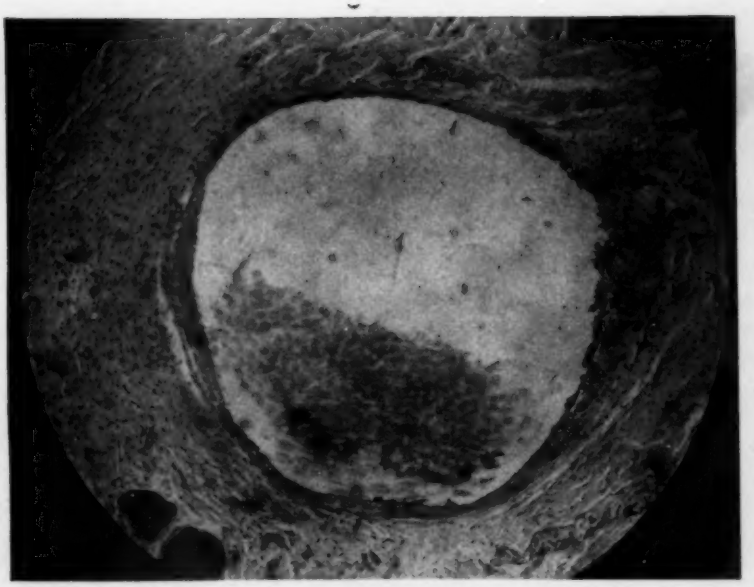
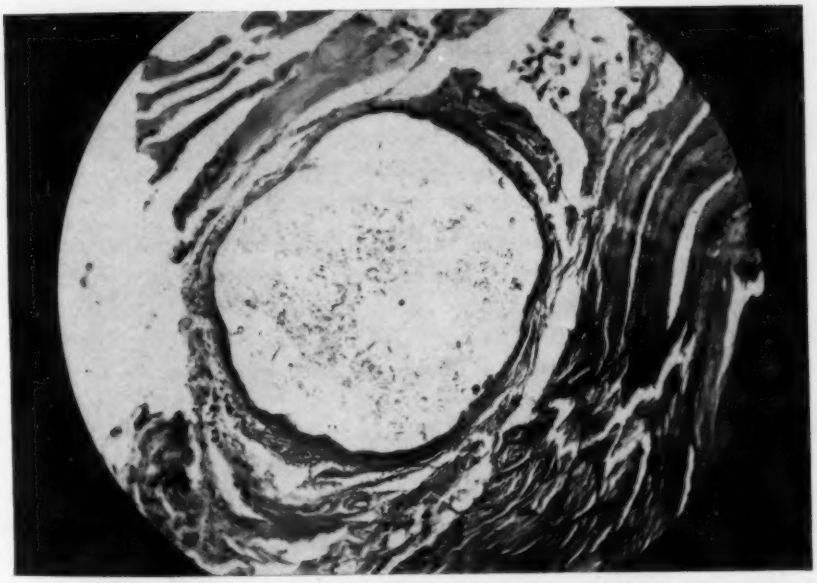


B

Fig. 4.—*A*, section of plastigut six weeks after exposure to an infected field. The guinea pig chewed off its skin suture, and the incision had to be resutured with wire the next day. The infection which resulted has now subsided, and the suture has healed in. In spite of the marked infection around the suture there has been no tendency whatever for inflammatory invasion into the suture. There is no capillarity. *B*, section of plastigut at six months. There is no reaction, no inflammation and no capillarity.

A



B

Fig. 5.—*A*, plastigut at one year in a human being. There is no retained infection within the suture from capillarity, and no evidence of infection is present in the surrounding tissues. This demonstrates positively that the suture remains a nonreacting foreign body without adversely affecting the surrounding normal tissues. *B*, plastigut after two years and three months in a human being. No inflammatory reaction and no capillarity can be observed. This confirms once more the nonreacting character of the suture.

large. I frequently used the equivalent of no. 2 double as a continuous suture, both in clean and in infected wounds. Of 335 clean wounds, 7 showed localized reactions from mechanical irritation, and some of these required a secondary procedure to remove the cause of the irritation.

These figures require further clarification in relation to changing technic (see table).

It is obvious that the technic in the second group (use of fine sizes and single thread) has eliminated mechanical irritation almost to the point of extinction in clean wounds and has materially reduced "stitch trouble" in infected or contaminated wounds. I am convinced that this mechanical irritation arises from sutures of large bulk and from large knots. All others healed by first intention and have apparently remained healed. Since I have adopted single threads and small sizes up to size 0, whether continuous or interrupted, healing has been primary in all but 1 case.

Results with Plastigut

	Clean Wounds	Stitch or Sinus Trouble	Percentage	Infected or Contaminated Wounds	Stitch or Sinus Trouble	Percentage
First Group Continuous no. 2 plastigut, double or single	105	6	5.7	21	10	47.6
Second Group Continuous or interrupted no. 0000 to no. 0 plastigut, single	230	1	0.435	50	9	18.00

In a three year experience with plastigut I have encountered about all the complications that are possible with the suture. I have studiously tried to analyze my experiences and am now convinced that a certain technic should accompany its use. I am impressed by one observation —that continuous sutures within the peritoneal cavity can be used with impunity. I have observed no intraperitoneal complications following use of the continuous suture in either clean or infected wounds. There are no objections, however, to the use of interrupted intraperitoneal sutures. For clean wounds, extraperitoneal sutures may be continuous or interrupted. Generally speaking, interrupted sutures are preferable. The incisions heal promptly by primary intention, with no evidence of reaction, and the skin and underlying tissues during the period of healing remain pliable. For infected wounds and in cases of drainage interrupted suture technic is compulsory for extraperitoneal locations. I am convinced that the advocates of the Halsted silk technic will now find an almost ideal material in plastigut. In infected wounds, there is a definite tendency for the infection to localize without the spreading infection I so frequently observed with catgut. The inter-

rupted loops of plastigut will become loosened when uprooted by a slough and in most cases will be cast off with the slough. Occasionally it may be necessary to use a hook for a loop that has become loosened but not cast off. Those sutures which have become buried in viable tissues remain buried and cause no trouble. I am convinced that no sizes above no. 0 or, at most, no. 1 should be used and that all strands should be used single. The most useful range of sizes in my work has been between no. 0000 and no. 00. The strands are tough; they have a substantial "feel" equal to that of catgut and superior to the limpness of fine silk. Those who are advocates of the Halsted silk technic will find an improved substitute in a relatively heavier, relatively stronger, nonreacting, nonabsorbable suture that has all the advantages of silk without its disadvantages.

During the period of its development plastigut was supplied to a limited number of well known surgeons for clinical trial. All responses to a questionnaire after clinical trial were eminently and unanimously favorable to plastigut.

My convictions are based primarily on clinical application and results and are further supported by considerable experimental and microscopic evidence of the general utility and nonreacting qualities of the new suture.

SUMMARY

The choice of a suture should depend on a study of clinical and microscopic effects on wound healing.

Sutures should be classified as reacting and nonreacting.

Five principal factors have been enumerated in the production of a reacting effect. In the light of this study, all sutures in current use are inherently reacting foreign bodies.

A nonreacting foreign body will induce little or no inflammatory or irritating reaction.

The ideal properties in a suture are postulated.

Plastigut, a new suture, closely incorporates the ideal properties of a universal suture.

Plastigut is a nonreacting, nonabsorbable, noncapillary suture in which the essential components are synthetic plastics.

Extensive experimental and clinical studies have, in my opinion and in that of others, verified the claims for plastigut.

The technic with plastigut is described.

Plastigut represents a suture based on a newly emphasized principle of a nonreacting foreign body.

Plastigut is obtainable from the Plastigut Foundation, 428 Jefferson Building, Peoria, Ill.

The original work was performed in collaboration with Dr. Andrew C. Ivy, Professor of Physiology, Northwestern University.

RECURRENCE OF INFECTION AFTER ELECTIVE OPERATIONS IN CASES OF HEALED SUPPURATION IN BONES AND JOINTS

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Elective operative procedures in cases of healed suppuration in bones and joints are frequent in the practice of the orthopedic surgeon. The frequency with which osteomyelitis or suppurative arthritis recurs as a result of common, everyday trauma is only too well known. Operative trauma, such as that associated with arthrodesis, arthroplasty or osteotomy, is little different from closed external trauma. One should, therefore, expect some recurrence of infection in healed suppurative lesions of bones and joints in the event of operation. Actually, such recurrent infection has been observed for a number of years, and the frequency with which suppuration recurs was the impetus for this analysis. According to Wilensky,[1] destruction of trabeculae and subsequent hemorrhagic exudate result in an area of decreased resistance that can readily become infected with any available bacteria. The latency of osseous infection is a common disturbing factor, and there are frequently available bacteria in the operative area to produce the recurrent infection. Fraser [2] and others have cited instances of long delayed recurrence of infection. In 1 case a bone abscess remained closed for thirty-eight years. I have observed 1 case in which a closed bone abscess remained quiescent for four years and was discovered only during an elective osteotomy.

The material contained in this report was obtained from the service of Dr. Arthur Steindler, of the University of Iowa. The series analyzed consists of all the operations on healed suppurative areas in bones and joints that have been done in this clinic up to January 1940. A total of 215 operations was reviewed and serves as a basis for the conclusions to be drawn from this analysis. These procedures are divided, first, into an etiologic classification consisting of: (1) operations for gonorrheal arthritis; (2) operations for suppurative arthritis; (3) operations for hematogenous osteomyelitis, and (4) operations for

From the Department of Orthopedic Surgery (service of Dr. A. Steindler), the State University of Iowa Hospitals.

1. Wilensky, A. O.: Osteomyelitis, New York, The Macmillan Company, 1934.

2. Fraser, J.: Acute Osteomyelitis, Brit. M. J. **2**:605-610 (Oct. 4) 1924.

traumatic osteomyelitis. Suppurative arthritis needs a little defining in that under this heading are included only cases of articular involvement in which there was no osseous involvement. It is classified in this way because suppurative arthritis with regional osteomyelitis has all the characteristics of regular osteomyelitis. Likewise, the term traumatic osteomyelitis needs to be clarified, since under this heading are included only those cases in which the infection resulted from compound wounds of bone.

The cases were next divided into two classes depending on whether operation was performed immediately through the area of the previous suppuration or near it but not through it. This distinction is of considerable importance, as will be shown later. No attempt was made to correlate the type of operation with the recurrence of infection, since no case was accepted for analysis in which the operation did not constitute a major traumatic event to the bone. The most common procedures were arthroplasty, arthrodesis, osteotomy and bone graft. The cases were investigated from the standpoint of duration of activity of the infectious process, number of years the infectious process had been quiescent, age, sex, roentgen appearance and bacteria when available.

GONORRHEAL ARTHRITIS

This condition is included in this analysis because it is on occasion associated with frank suppuration in joints and because the causative organism is a notoriously good pus producer in other locations. The

TABLE 1.—*Gonorrheal Arthritis*

Average Age, Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent	Recurrence
26	0.1-1.5	0.6	0.5-14	3.2	None

patients were 7 men and 20 women. Twenty-seven cases were reviewed. The location of the process was as follows: knee, 14 cases; hip, 3 cases; hand, 1 case; elbow, 6 cases; foot, 3 cases. One patient in this group had a typical postoperative wound infection with Staphylococcus albus, but as such it did not represent a recurrence of the original infection. All the operations were done directly into the old healed articular areas, and all included work on bone; yet, in spite of this and the fact that in some instances the areas had been healed for only six months, there still were no recurrences of infection. From this series it would appear that healed gonorrheal joints can be operated on with little, if any, danger of recurrence and at almost any time the operator desires.

SUPPURATIVE ARTHRITIS

This group includes all cases of healed purulent articular infection without associated osteomyelitis. Eighty-three cases were reviewed, and in 48 instances the operation was performed through the previously involved joint, while in 35 instances the operation was performed near but not through the previously involved joint.

The statistics on the exactly located operations, after which infection did not recur, are as follows: cases, 42; male patients, 18; female patients, 24. Location: knee, 24 cases; hip, 12 cases; elbow, 6 cases.

The statistics on the exactly located operations after which infection did recur are as follows: cases, 6; male patients, 4; female patients, 2. Location: hips, 3 cases; knee, 3 cases.

TABLE 2.—*Nonrecurrent Suppurative Arthritis in Operative Area*

Age, Years	Average Age, Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent
3-40	21.7	0.1-4	0.6	0.5-24	4

TABLE 3.—*Recurrent Suppurative Arthritis in Operative Area*

Age, Years	Average Age, Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent
17-60	30	0.1-1	0.6	1-30	Over 11

There is little difference between the general statistics in these two series. The quiescent period was longer in cases of recurrent than in those of nonrecurrent infection. This bears out the contention that the time of quiescence is not the important factor in recurrence of infection in healed suppurative arthritis when it is operated on. This fact has been previously pointed out by Steindler.[3] The contrast of the 6 cases of recurrence to the total of 48 cases gives a recurrence rate of 13 per cent. The recurrent bacterium in this series was the staphylococcus in all but 1 case, in which it was the streptococcus. The duration of the recurrent infection varied from three-tenths year to eleven years, with an average of three and five-tenths years. This, then, constitutes a complication to be avoided when possible. The percentage of recurrence in this series corresponds closely to that reported by Hallock[4] of 2

3. Steindler, A.: Orthopedic Operations, Springfield, Ill., Charles C. Thomas, Publisher, 1940.

4. Hallock, H.: Study and End Results of Seventy Arthroplasties and Reconstruction Operations on Hip Joint, Surg., Gynec. & Obst. **68**:106-112 (Jan.) 1939.

cases in 20 operations; in 1 of these the infection had been quiescent for five years and showed a Staph. aureus on culture at the time of operation.

The statistics on operations done, near healed suppurative joints in which the infection did not recur are as follows: cases, 32; male patients, 23; female patients, 9. Location: hips, 23 cases; knee, 9 cases.

TABLE 4.—*Nonrecurrent Suppurative Arthritis Near Operative Area*

Age, Years	Average Age, Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent
3-47	32	0.1-10	2	0.4-36	15

TABLE 5.—*Recurrent Suppurative Arthritis Near Operative Area*

Age, Years	Average Age, Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent
13-18	16	0.8-3	1.4	1-15	6

TABLE 6.—*Nonrecurrent Hematogenous Osteomyelitis in Operative Area*

Age, Years	Average Age, Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent
1.5-47	16	0.2-5	1	1-36	6.4

TABLE 7.—*Recurrent Hematogenous Osteomyelitis in Operative Area*

Age, Years	Average Age, Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent
10-51	21	0.1-6	1.5	1-9	2.5

The statistics on operations done near to healed suppurative joints in which the infection did recur are as follows: cases, 3; male patients, 2; female patients, 1. Location: hips in all cases.

The percentage of recurrence of infection in these suppurative joints operated on near but not through the previous involved area is, then, 8 per cent. The time required for the secondary healing varied from three-tenths year to one year. This group of operations performed near areas of previous infection, contrasted to the exactly located operations, shows a slightly less frequency of recurrence but a much shorter period of secondary healing time.

HEMATOGENOUS OSTEOMYELITIS

Seventy-six operations were analyzed in this group; of these, 35 were performed in the previously involved area and as such are classified as exactly located operations, while 41 were performed near the involved area but not through it and as such are classified as neighboring operations.

The statistics on the exactly located operations after which the infection did not recur are: cases, 19; male patients, 12; female patients, 7. Location: hip, 9 cases; knee, 4 cases; tibia, 3 cases; femur, 1 case; wrist, 1 case; tarsus, 1 case.

The statistics on the exactly located operations after which the infection did recur are: cases, 16; male patients, 7; female patients, 9. Location: hip, 6 cases; knee, 3 cases; tibia, 3 cases; femur, 2 cases; ankle, 1 case; astragalus, 1 case.

The analysis of these two sets of statistics shows little variance. The quiescent period was longer in cases of recurrent than in cases of non-

TABLE 8.—*Nonrecurrent Hematogenous Osteomyelitis Near Operative Area*

Age, Years	Average Age, Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent
2-48	18	0.1-14	2	0.5-33	5

recurrent infection, but there were periods as long as nine years of quiescence followed by recurrence, which again bears out the contention that time alone cannot be used as a criterion for elective operative intervention in cases of healed osteomyelitis. The recurrences were again preponderantly staphylococcic, with only 1 instance of streptococcic infection. The recurrent complications lasted from two-tenths year to twelve years, with an average of two and nine-tenths years. The contrast of these two groups gives a rate of recurrence of infection of 46 per cent for operations at the site of previously healed osteomyelitis.

The statistics on the operations done near areas of healed osteomyelitis that did not recur are: cases, 40; male patients, 17; female patients, 23. Location: hip, 33 cases; tibia, 3 cases; knee, 3 cases; tarsus, 1 case.

There was only 1 case of recurrence in the operations performed in a neighboring area of this group, and this occurred in a 39 year old man. The infection had been active for twenty years and quiescent for six months; it recurred for eighteen months. Contrasting this 1 case with the 40 cases in which infection did not recur shows a recurrence of 2.5 per cent. This is in marked contrast to 46 per cent of recurrence when the operation was carried out through the previously involved

area. Steindler has previously called attention to this low frequency of recurrence of osteomyelitis when the operation is carried out away from the area of healed osteomyelitis.

TRAUMATIC OSTEOMYELITIS

In all of the cases in this group operation was done through the previously osteomyelitic area and so fall into two groups: first, those in which the infection recurred and, second, those in which it did not.

First group (recurrences): cases, 8; male patients, 6; female patients, 2. Location: tibia, 6 cases; ankle, 1 case; femur, 1 case.

Second group (nonrecurrent infections): cases, 21; male patients, 14; female patients, 7. Location: forearm, 8 cases; tibia, 7 cases; humerus, 4 cases; tarsus, 1 case; fibula, 1 case.

TABLE 9.—*Recurrent Traumatic Osteomyelitis in Operative Area*

Age, Years	Average Age, Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent
5-53	28	0.2-4	1.2	0.4-9	2.4

TABLE 10.—*Nonrecurrent Traumatic Osteomyelitis in Operative Area*

Age, Years	Average Age, Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent
6-53	24	0.3-4	1.1	0.4-16	3.5

The contrast of these two groups shows little variance in the general statistics. There was a 28 per cent recurrence of infection. The secondary recurrent complication lasted from three-tenths year to six years, with an average of two years. Here, as in the previous groups, the time of quiescence is not related to the recurrence. This has been emphasized by Watson-Jones,[5] who recommended a six month quiescent period before operation.

ROENTGEN APPEARANCE

Roentgenograms were investigated in an effort to determine criteria that would indicate recurrence of infection in the event of operative trauma at the site of previous suppuration in bones and joints. When all of the cases in which bone was involved were removed from the group of cases of suppurative arthritis, there was a group of 11 cases of true suppurative arthritis in which there was roentgen evidence of suppura-

5. Watson-Jones, R.: Fractures and Other Bone and Joint Injuries, Baltimore, Williams & Wilkins Company, 1940.

tion confined to the joints alone and in which there was no recurrent infection. Figure 1 shows an example of this condition. This is in harmony with the finding of the low percentage of recurrence of infection in cases of suppurative arthritis in the general statistics. The discrepancy between the number of cases studied by roentgenograms and those studied by case histories is due to the fact that the roentgenograms were available for only ten years, while the histories were available for twenty-five.

Fig. 1.—Roentgenogram in a case of pure suppurative arthritis. There is no evidence of involvement of bone, and all destruction has been confined to the joint.

The most imminent problem concerns the decision as to when to operate on an area of healed osteomyelitis. There are a number of roentgen findings that are evidence of infectious involvement of bone. Obviously, no cases were seen in this group of osteomyelitis in which the acute bone destruction of acute osteomyelitis was present, but in all cases there was evidence of healed or healing osteomyelitis. The roentgenograms were investigated from the standpoint of sequestrums, arrangement of trabeculation and density. The amount of sclerosis or increased density

was always directly proportional to the immaturity of the trabeculae. The appearance of normal trabeculae is evidence of the fact that the original involucrum or osteoblastic apposed bone has been reworked into normal bone through the demands of stress and strain. Sequestrums, no matter how small, must be interpreted as evidence of infection, since a sequestrum is either surrounded by pus, in which event it persists indefinitely, or it is surrounded by granulation tissue, in which event it is being slowly absorbed. The rate of absorption is relative to the size of the sequestrum, the blood supply and the density of the surrounding bone. Close examination of roentgenograms of areas of healed osteomyelitis, particularly with a magnifying lens, will often disclose sequestrums that are not observed on a less detailed search. A small sequestrum has the same appearance as a larger one, namely, an area of increased density surrounded by an area of porosis, the whole being surrounded by dense bone. The inner dense body is the sequestrum, and the porotic area represents the pus or granulation. The whole is surrounded by sclerotic bone.

There were 14 cases of healed osteomyelitis in which operation was performed through the site of the previous infection and in which roentgenograms were available for study. These 14 cases fell into three classifications when the sequestrums, trabeculations, density and recurrence of infection were considered.

Group I (fig. 2).—Four cases, in which there were normal trabeculations, normal density, no sequestrums and no recurrence of infection.

Group II (fig. 3).—Five cases, in which there were abnormal trabeculations, increased density, no sequestrums, and recurrence of infection in 60 per cent.

Group III (fig. 4).—Five cases, in which there were abnormal trabeculations, increased density, the presence of sequestrums and recurrence of infection in 100 per cent.

From these groups it is then seen that the presence of sequestrums in the operative field is indicative of recurrent infection. Abnormal trabeculations, the characteristic of the second group, must be considered as a danger sign, since in 60 per cent of this group infection recurred. The normal-appearing bone in the first group represents areas of healed osteomyelitis that can be operated on without recurrence of infection. It then appears that the more nearly the osteomyelitic bone has reconstructed itself to normal, the less chance is there of recurrence of infection.

Roentgenograms in 14 cases of healed traumatic osteomyelitis were also investigated, but it was impossible to form a correlation between the roentgen appearance and the recurrence of infection.

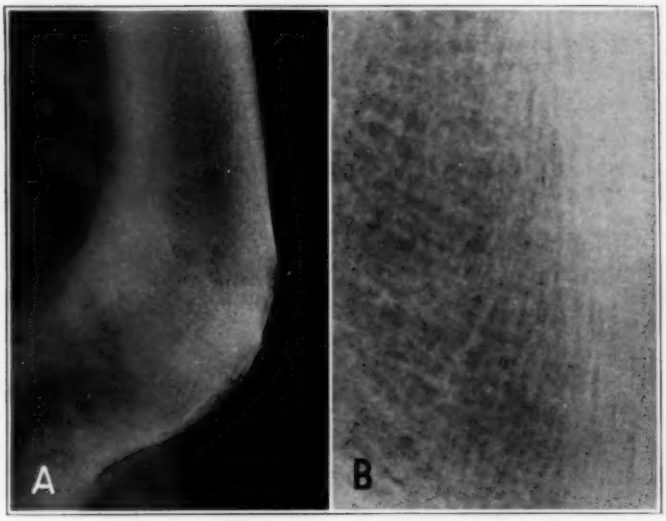

Fig. 2.—*A*, roentgenogram of a knee that was operated on through the supracondylar area. This is an example of group I in the roentgen classification of healed osteomyelitis. This is the type that does not recur and is characterized by normal trabeculation, no sequestrums and normal density. The enlargement (*B*) shows the characteristics in detail.

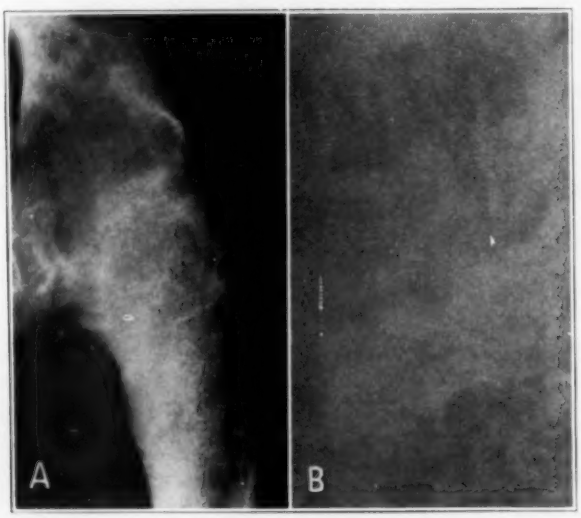

Fig. 3.—*A*, roentgenogram of healed osteomyelitis in a patient operated on in the hip joint area. It is an example of group II in the roentgen classification of healed osteomyelitis. This group is characterized by abnormal trabeculations, no sequestrums and sclerosis with recurrence in 60 per cent of cases. The enlargement of the joint surface (*B*) shows the abnormal trabeculae in detail.

CONCLUSIONS

1. Gonorrheal arthritis, once it is healed, does not recur after operative trauma. Subsidence of the acute infection and return to the normal afebrile state for six months should be a sufficient interval.

2. Pure suppurative arthritis, when healed, recurs in only 13 per cent of cases when operation is performed through the previously involved area.

Fig. 4.—*A*, roentgenogram showing healed osteomyelitis of the tibia and ankle. In this case operation was done in the ankle area. It is an example of group III in the roentgen classification; that is, the group characterized by abnormal trabeculation, sclerosis, sequestrums and recurrence in all cases. The enlargement (*B*) shows the numerous small sequestrums indicative of recurrent infection.

3. Hematogenous osteomyelitis, when operation is performed through the previously involved area, recurs in 46 per cent of cases.

4. Operations carried out near but not through an area of previous osteomyelitis or suppurative arthritis carry a very low frequency of

recurrence of the infection. This was 2.5 per cent for osteomyelitis and 8 per cent for suppurative arthritis in the present study.

5. The time for which the infectious process has been quiescent has no relation to the recurrence of infection.

6. By careful analysis of the roentgen appearance of healed osteomyelitis it is possible to anticipate which infections will recur in the event of surgical intervention.

7. The complication of recurrence is a major affair and should be avoided whenever possible.

RECURRENT INGUINAL HERNIAS

A STUDY OF TWO HUNDRED AND EIGHTY-TWO HERNIAS AND TWO HUNDRED AND SIXTY-EIGHT REPAIRS

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This study covered 282 recurrent inguinal hernias, of which 268 were repaired.[1] Included were all hernias of this type in patients admitted to the wards of St. Luke's Hospital, New York, from 1926 to 1935 and all repaired between 1916 and 1925 and followed postoperatively for nine months or longer. They comprised 6.4 per cent of all hernias for these two periods and 7.7 per cent of the total inguinal hernias.

Of the 268 hernia repairs, 210 were observed postoperatively for nine months or longer (the average follow-up time was thirty-eight and four-tenths months). Among these were found 39 recurrences, giving an incidence of recurrence of 18.6 per cent. The average postoperative time after which these recurrences were first noted was nineteen and six-tenths months. Only 3 (7.7 per cent) of these recurrences were indirect, and 36 (92.3 per cent) were direct.

ETIOLOGIC FACTORS

Age at Onset (Age at which Hernia was First Noted).—This was necessarily determined by the ages of the patients when their hernias were first repaired and the elapsed time between repair and the time at which the recurrences were first noted. Consequently, a table giving the various age incidences was not considered to be of any particular value.

Indirect Inguinal Recurrences: The average age of the patients when the indirect recurrences were first noted was 36.7 years, as compared with 30.9 years for patients with primary incomplete indirect inguinal hernias[1a] and 9 years for patients with complete indirect inguinal hernias.[1b]

From the Surgical Services of St. Luke's Hospital.

1. All references to types of hernias other than recurrent inguinal hernias are from the following papers published by me: (*a*) Incomplete Indirect Inguinal Hernias: A Study of 2,462 Hernias and 2,337 Repairs, Arch. Surg. **41**:747-771 (Sept.) 1940; (*b*) Complete Indirect Inguinal Hernias: A Study of 305 Hernias and Repairs, South. Surgeon **9**:257-268 (April) 1940; (*c*) Direct Inguinal Hernias: A Study of 605 Hernias and 565 Repairs, Arch. Surg. **41**:857-872 (Oct.) 1940; (*d*) Femoral Hernias: A Study of 238 Hernias and 226 Repairs, ibid. **41**:1229-1243 (Nov.) 1940; (*e*) Ventral Hernias: A Study of 550 Hernias and 458 Repairs, South. Surgeon **9**:617-656 (Sept.) 1940.

Direct Inguinal Recurrences: The average age at which the direct recurrences were first noted was 42.8 years. This age is two years greater than the average age, 40.8 years, at which primary direct inguinal hernias were first noted, but it is less than the average age, 43.7 years, at which the primary repairs were performed.[1e] The reasons for this

TABLE 1.—*Indirect Inguinal Recurrences: Age at Time of Admission or Operation*

Age Group (Years)	Total Hernias	Per Cent of Entire Group		Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	
0 to 10	1	0.8	3.9	1	1	100.0	100.0
10 to 20	4	3.1		2	2	100.0	
20 to 30	33	25.8	48.4	26	2	7.7	10.4
30 to 40	29	22.6		22	3	13.6	
40 to 50	29	22.6	42.9	20	2	10.0	7.7
50 to 60	26	20.3		19	1	5.3	
60 to 70	6	4.7	4.7	5	0	0.0	0.0
Totals	128	100.0	100.0	95	11	11.6	11.6

The average age of the patients at time of admission or operation for indirect inguinal recurrences was 39.6 years.

TABLE 2.—*Direct Inguinal Recurrences: Age at Time of Admission or Operation*

Age Group (Years)	Total Hernias	Per Cent of Entire Group		Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	
0 to 10	0	0.0	0.0	..	..	....	....
10 to 20	0	0.0		..	..	....	
20 to 30	11	7.1	31.3	9	2	22.2	18.0
30 to 40	38	24.2		30	5	16.7	
40 to 50	55	35.5	58.1	42	12	28.6	27.5
50 to 60	35	22.6		27	7	25.9	
60 to 70	14	9.0	9.7	6	2	33.3	28.6
70 to 80	1	0.7		1	0	0.0	
Totals	154	100.0	100.0	115	28	24.4	24.4

The average age at the time of admission or operation for direct inguinal recurrences was 45.4 years.

are: 1. A considerable number of direct recurrences followed repairs of indirect hernias and indirect recurrences. 2. Not all the recurrences in the older patients were repaired.

Age at Time of Admission or Operation.—Indirect Inguinal Recurrences: The average age at the time of operation for these hernias was 39.6 years. This compared with 34.8 years for primary incomplete hernias and 16.2 years for complete indirect inguinal hernias. The age incidences were distributed fairly evenly in the decades from 20 to 60

years, ranging from 25.8 to 20.3 per cent. In all 3 repairs on patients under 20 years of age which were followed for nine months or longer, recurrences developed. This might indicate that not sufficient importance was attributed to this condition in young patients and that consequently inadequate repairs were done. Recurrences developed in 10.4 per cent of patients between the ages of 20 and 40 and in 7.7 per cent between 40 and 60 years. This difference might also be due to the reason just suggested.

Direct Inguinal Recurrences: The average age at the time of admission or operation for direct recurrences was 45.4 years. This was one and seven-tenths years greater than the corresponding figure for primary

TABLE 3.—*Indirect Inguinal Recurrences: Sex Incidence*

Sex	Total Hernias	Per Cent of Entire Group	Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences
Male	115	89.8	84	11	12.4
Female	13	10.2	11	0	0.0
Totals	128	100.0	95	11	11.6

TABLE 4.—*Direct Inguinal Recurrences: Sex Incidence*

Sex	Total Hernias	Per Cent of Entire Group	Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences
Male	145	94.3	108	26	24.1
Female	9	5.7	7	2	28.6
Totals	154	100.0	115	28	24.4

direct inguinal hernias, 43.7 years, and five and eight-tenths years greater than that for indirect inguinal recurrences, 39.6 years.

No repairs were done on patients under 20 years of age. Thirty-one and three-tenths per cent of the patients were between 20 and 40, 58.1 per cent between 40 and 60 and 9.7 per cent between 60 and 80. The recurrence incidence showed an increase with the patients' ages at the time of operation, as follows: up to 20, no repair; 20 to 40, 18 per cent; 40 to 60, 27.5 per cent, and 60 to 80, 28.6 per cent.

Sex.—Indirect Inguinal Recurrences: The sex incidence among patients with indirect inguinal recurrences, males 89.8 per cent and females 10.2 per cent, was essentially the same as that found in patients entering the hospital during the same period for original repairs of incomplete indirect inguinal hernias, males 88.7 per cent and females 11.3 per cent. The number of females in this group was too small for the absence of recurrences to have any definite significance.

Direct Inguinal Recurrences: The percentage of males in this group, 94.3 per cent, was slightly less than in the group with primary direct inguinal hernias, 96.9 per cent. The percentage of recurrences was practically the same in male and female patients, 24.1 per cent for males and 28 6 per cent for females, after repair of direct inguinal recurrences, as contrasted to 15.2 per cent for males and 5.5 per cent for females after repair of primary direct inguinal hernias.

Race.—Indirect Inguinal Recurrences: As with the race incidence among the admissions for primary repairs of incomplete indirect inguinal hernias, that for indirect inguinal recurrences, white 93.8 per cent and Negro 6.2 per cent, checked with the racial incidence of general admissions to the hospital.

TABLE 5.—*Indirect Inguinal Recurrences: Race*

Race	Total Hernias	Per Cent of Entire Group	Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences
White	120	93.8	91	11	12.1
Negro	8	6.2	4	0	0.0
Totals	128	100.0	95	11	11.6

TABLE 6.—*Direct Inguinal Recurrences: Race*

Race	Total Hernias	Per Cent of Entire Group	Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences
White	151	98.1	114	28	24.5
Negro	3	1.9	1	0	0.0
Totals	154	100.0	115	28	24.4

Direct Inguinal Recurrences: The preponderance of white patients in this group, 98.1 per cent, was greater than that found in the case of either primary direct inguinal hernias, 94.7 per cent, or indirect inguinal recurrences, 93.8 per cent.

The numbers of Negro patients in both groups were too small for the absence of recurrences to have any particular significance.

Trauma.—Indirect Inguinal Recurrences: The figures for the incidence of a history of definite trauma as the etiologic factor in these indirect inguinal recurrences (no such history in 73.4 per cent and the presence of such a history in 26.6 per cent) checked exactly with the corresponding figures for the primary incomplete indirect inguinal hernias. As with repair of the latter type of hernias, the incidence of recurrence following repair of indirect inguinal recurrences was definitely less when the history of a traumatic cause was given, 8.3 per cent, as contrasted to

an incidence of 12.7 per cent when no such history was given (see footnote to table 7).

Direct Inguinal Recurrences: The incidence of definite trauma given as the cause of the direct inguinal recurrences was one third less, 20.1 per cent, than that for primary direct hernias, 31.4 per cent. The recurrence rate, 29.6 per cent, in the presence of a definite history of trauma was slightly greater than when such a history was absent, 22.7 per cent.

TABLE 7.—*Indirect Inguinal Recurrences: History of Definite Trauma as Etiologic Factor* *

History of Trauma as Cause *	Total Hernias	Per Cent of Entire Group	Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences
Absent	94	73.4	71	9	12.7
Positive *	34	26.6	24	2	8.3
Totals	128	100.0	95	11	11.6

* Undoubtedly all or a major part of these hernias were present before the incidence of the trauma, which served only to call the patients' attention to the presence of the hernia. In this connection it is interesting to note that among the 305 complete (congenital) indirect inguinal hernias studied, a history of definite trauma as the etiologic factor was given by 26 per cent of the patients who first noticed their hernias after the age of 15 (Shelley, H. J.: Complete Indirect Inguinal Hernias: A Study of 305 Hernias and Repairs, South. Surgeon 9: 257-268 [April] 1940).

TABLE 8.—*Direct Inguinal Recurrences: History of Definite Trauma as Etiologic Factor* *

History of Trauma as Cause *	Total Hernias	Per Cent of Entire Group	Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences
Absent	123	79.9	88	20	22.7
Positive *	31	20.1	27	8	29.6
Totals	154	100.0	115	28	24.4

* Undoubtedly all or a major part of these hernias were present before the incidence of the trauma, which served only to call the patients' attention to the presence of the hernia. In this connection it is interesting to note that among the 305 complete (congenital) indirect inguinal hernias studied, a history of definite trauma as the etiologic factor was given by 26 per cent of the patients who first noted their hernias after the age of 15 (Shelley, H. J.: Complete Indirect Inguinal Hernias: A Study of 305 Hernias and Repairs, South. Surgeon 9: 257-268 [April] 1940).

This is in contrast to lower recurrence rates when a history of traumatic causation was given with the primary indirect and direct and recurrent indirect inguinal hernias (see footnote to table 8).

SYMPTOMS

Pain.—Indirect Inguinal Recurrences: A history of the association of pain with these recurrent hernias was somewhat higher, 60.1 per cent, than that given for the primary incomplete indirect inguinal hernias, 49.7 per cent.

Direct Inguinal Recurrences: Essentially the same proportion of the direct recurrences were the cause of pain, 49.3 per cent, as was the case with primary direct inguinal hernias, 52.2 per cent.

TABLE 9.—*Indirect Inguinal Recurrences: History of Pain Associated with Hernia*

History of Pain	Total Hernias	Per Cent of Entire Group
Absent	51	39.9
Positive	77	60.1
Totals	128	100.0

TABLE 10.—*Direct Inguinal Recurrences: History of Pain Associated with Hernia*

History of Pain	Total Hernias	Per Cent of Entire Group
Absent	78	50.7
Positive	76	49.3
Totals	154	100.0

TABLE 11.—*Indirect Inguinal Recurrences: Duration (Time Hernia Was First Noted to Time of Admission or Operation)*

Duration	Total Hernias	Per Cent of Entire Group	Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences
To 1 week	11	8.6	5	0	0.0
To 1 month	25	19.5	15	2	13.3
First 6 months	58	45.3	42	7	16.7
Second 6 months	24	18.7	18	2	11.1
To 1 year	82	64.1	60	9	15.0
0 to 5 years	107	83.6	81	9	11.1
5 to 10 years	12	9.4	7	0	0.0
0 to 10 years	119	92.9	88	9	10.2
10 to 20 years	6	4.7	4	2	50.0
20 to 30 years	2	1.6	2	0	0.0
30 to 40 years	0	0.0	..	..	....
40 to 50 years	1	0.8	1	0	0.0
Totals	128	100.0	95	11	11.6

The average duration (elapsed period from the time the hernia was first noted to time of operation) of indirect inguinal recurrences was 2.9 years.

TABLE 12.—*Direct Inguinal Recurrences: Duration (Time Hernia Was First Noted to Time of Admission or Operation)*

Duration	Total Hernias	Per Cent of Entire Group	Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences
To 1 week	8	5.2	7	2	28.6
To 1 month	26	16.9	21	7	33.3
First 6 months	56	36.4	46	13	29.6
Second 6 months	24	15.6	17	0	0.0
To 1 year	80	52.0	63	13	20.6
0 to 5 years	127	82.5	95	23	24.2
5 to 10 years	12	7.8	9	3	33.3
0 to 10 years	139	90.3	104	26	25.0
10 to 20 years	13	8.5	10	2	20.0
20 to 30 years	1	0.7	0	..	....
30 to 40 years	1	0.7	1	0	0.0
Totals	154	100.0	115	28	24.4

The average duration (elapsed period from the time the recurrence was first noted to time of admission or operation) of direct inguinal recurrences was 2.6 years.

Duration.—Indirect Inguinal Recurrences: The average elapsed time from the discovery of these recurrences to the time of operation was two and nine-tenths years as compared with three and nine-tenths years for the primary incomplete indirect inguinal hernias.

Direct Inguinal Hernias: The average duration of the direct recurrences was two and six-tenths years as compared with two and nine-tenths years for the primary direct hernias.

TABLE 13.—*Indirect Inguinal Recurrences: Size*

Size of Hernia *	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Operative Deaths (1926-1935)	Per Cent Mortality
Size I.....	36	28.1	22	1	4.5	0 in 31 operations	0.0
Size II.....	47	36.7	38	8	21.2	0 in 31 operations	0.0
Size III....	45	35.2	35	2	5.7	0 in 24 operations	0.0
Totals...	128	100.0	95	11	11.6	0 in 86 operations	0.0

* Size I: Hernias in which the sac was limited in extent to the inguinal canal.
Size II: Hernias in which the sac extended beyond the external ring but not into the scrotum.
Size III: Hernias in which the sac extended into the scrotum.

TABLE 14.—*Direct Inguinal Recurrences: Size*

Size of Hernia *	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Operative Deaths (1926-1935)	Per Cent Mortality
Size I.....	57	37.0	44	7	15.7	1 in 37 operations †	2.7
Size II.....	66	42.9	50	13	26.0	0 in 37 operations	0.0
Size III....	31	20.1	21	8	38.1	1 in 13 operations †	7.6
Totals...	154	100.0	115	28	24.4	2 in 87 operations †	2.3

* Size I: Hernias in which the sac was limited to the inguinal canal.
Size II: Hernias in which the sac extended beyond the external ring but not into the scrotum.
Size III: Hernias in which the sac extended into the scrotum.
† The hernias were not strangulated in either of the 2 patients who died postoperatively.

The numbers of followed repairs in the various durations of both types of recurrent hernias were too small to give any definite indications as to any effect the duration might have on the expectancy of recurrence after repair.

PHYSICAL FINDINGS

Size.—Indirect Inguinal Recurrences: The incidences of the three sizes (see table 13 for definition of the sizes) of these hernias were essentially the same as with the primary hernias. That the majority of the recurrences should have followed repair of hernias which extended beyond the external ring but not into the scrotum is not readily explained. However, in such small groups of followed repairs the recurrence rates are not necessarily accurate.

Direct Inguinal Recurrences: The sac of the direct inguinal recurrent hernia entered the scrotum in a larger proportion of instances, 20.1 per cent, than was found to be the case with the primary direct hernias, 12.4 per cent. Apparently the size of these recurrent hernias influenced the probability of a second recurrence after repair, as follows: sac limited to the inguinal canal, 15.7 per cent of recurrences; sac extending beyond the external ring but not into the scrotum, 26 per cent of recurrences, and scrotal hernias, 38.1 per cent of recurrences. The same was found true with the primary indirect and direct hernias, but without as great a difference.

TABLE 15.—*Indirect Inguinal Recurrences: Unilateral and Bilateral**

(A)

	Total Hernias	Per Cent of Entire Group	Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences
Unilateral, right	43	33.6	33	3	9.1
Unilateral, left	19	14.8	11	1	9.1
Total unilateral	62	48.5	44	4	9.1
Total bilateral	66	51.5	51	7	13.9
Total right	77	60.2	60	8	13.3
Total left	51	39.8	35	3	8.3
Totals	128	100.0	95	11	11.6

(B)

By original operation
Two sides repaired separately: recurrences, 9.5%
Two sides repaired at one operation: recurrences, 13.3%

By this operation
Two sides repaired separately: recurrences, 15.6%
Two sides repaired at one operation: recurrences, 5.3%

(C)

Recurrences: indirect, 10.0%; direct, 90.0%

* Each hernia was counted individually. Each indirect inguinal recurrence was considered one of two bilateral inguinal hernias when there was or had been an inguinal hernia of any type on the opposite side.

Unilateral and Bilateral Hernias.—All the hernias in this study were considered individually. A recurrent hernia was considered as one of two bilateral hernias when another inguinal hernia of any type was present at the same time, had been present previously or appeared later on the opposite side.

Indirect Inguinal Recurrences: The incidence of bilateral hernias in this group, 51.5 per cent, was definitely greater than that of the original incomplete indirect inguinal hernias, 32.7 per cent. This is readily understood, as the incidence of recurrences was approximately 50 per cent greater after repair of the original bilateral indirect hernias than after repair of the primary unilateral hernias. The same was observed after repair of bilateral indirect recurrences (13.9 per cent recurrences as compared with 9.1 per cent recurrences for the unilateral hernias).

Direct Inguinal Recurrences: The incidence of bilateral hernias in this group, 53.2 per cent, was not quite as large as was that found for primary hernias, 59.1 per cent. However, the increased recurrence rate, 27.7 per cent for bilateral hernias and 20 per cent for unilateral hernias, was more definite than that observed after repair of primary bilateral direct hernias, 15.4 per cent, as compared with 14.1 per cent for primary unilateral repairs.

TABLE 16.—*Direct Inguinal Recurrences: Unilateral and Bilateral* *

	Total Hernias	Per Cent of Entire Group	Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences
Unilateral, right.....	41	26.6	28	6	21.4
Unilateral, left.....	31	20.1	22	4	18.2
Total unilateral.....	72	46.8	50	10	20.0
Total bilateral.....	82	53.2	65	18	27.7
Total right.....	82	53.2	61	15	24.6
Total left.....	72	46.8	54	13	24.1
Totals.....	154	100.0	115	28	24.4

* Each hernia was counted individually. Each direct inguinal recurrence was considered one of two bilateral inguinal hernias when there was or had been an inguinal hernia of any type on the opposite side.

TABLE 17.—*Indirect Inguinal Recurrences: Incarceration and Strangulation*

Incarcerated or Strangulated	Total Hernias	Per Cent of Entire Group	Number Followed Postop-eratively	Number of Recur-rences	Per Cent Recur-rences	Operative Deaths (1926-1935)	Per Cent Mortality
Neither.....	116	90.7	87	9	10.3	0 in 78 operations	0.0
Incarcerated *	10	7.8	6	2	33.3	0 in 6 operations	0.0
Strangulated *	3	2.3	3	0	0.0	0 in 2 operations	0.0
Totals...	128	100.0	96	11	11.6	0 in 86 operations	0.0

* Strangulation developed in 1 old incarcerated hernia.

TABLE 18.—*Direct Inguinal Recurrences: Incarceration and Strangulation*

Incarcerated or Strangulated	Total Hernias	Per Cent of Entire Group	Number Followed Postop-eratively	Number of Recur-rences	Per Cent Recur-rences	Operative Deaths (1926-1935)	Per Cent Mortality
Neither.....	140	91.1	105	24	23.8	2 in 76 operations	2.6
Incarcerated.	8	5.1	6	1	16.7	0 in 8 operations	0.0
Strangulated *	6	3.8	4	3	75.0	0 in 3 operations	0.0
Totals...	154	100.0	115	28	24.4	2 in 87 operations	2.3

* Two patients who had strangulated hernias were not operated on, as they were moribund when admitted to the hospital. Both died.

Incarceration and Strangulation.—Indirect Inguinal Recurrences: The incidences of incarceration and strangulation were slightly greater for the recurrences, 7.8 and 2.3 per cent respectively, than for the primary hernias, 6 and 1.8 per cent respectively.

Direct Inguinal Recurrences: This increase was even more marked with the direct recurrences, 5.1 and 3.8 per cent, as compared with 3.1 and 1.6 per cent for primary direct inguinal hernias.

The numbers of hernias studied in the various groups of both types of recurrent hernias were too small for the respective recurrence rates to have any definite significance.

RESULTS ACCORDING TO TYPE OF REPAIR

Because of the relatively small numbers of followed cases with each of the various types of repairs, the recurrence rates are undoubtedly inaccurate. However, they are given in tables 19 and 20 for whatever they may be worth.

TABLE 19.—*Indirect Inguinal Recurrences: Type of Repair*

Type of Repair *	Total Followed	Per Cent Recurrences	Per Cent Infections †	Per Cent Infections Showing Recurrences †	Per Cent Recurrences	
					Indirect	Direct
1	4	25.0	0.0	...	0.0	100.0
2	36	11.1	2.8	0.0	25.0	75.0
2A	10	10.0	0.0	...	0.0	100.0
2B	14	7.1	42.8	0.0	0.0	100.0
3	3	33.3	0.0	...	0.0	100.0
4	8	37.5	12.5	0.0	0.0	100.0
4A	6	0.0	0.0	...	.....	.....
4B	4	0.0	0.0	...	.....	.....
5	9	0.0	0.0	...	.....	.....
6	1	0.0	0.0	...	.....	.....
All repairs without fascial sutures	61	14.8	4.9	0.0	11.1	88.9
All repairs with fascial sutures....	34	5.9	17.6	0.0	0.0	100.0
Totals.....	95	11.6	6.7	0.0	9.1	90.9

* Type 1: Repairs without transplantation of the cord.

Type 2: Repairs with transplantation of the cord between the conjoined tendon and the aponeurosis of the external oblique muscle.

Type 2A: Same as type 2, with suture of the conjoined tendon and the inguinal ligament with a fascial suture from the aponeurosis of the external oblique muscle.

Type 2B: Same as type 2, with suture of the conjoined tendon and the inguinal ligament with a fascial suture obtained from the fascia lata.

Type 3: Repairs with transplantation of the cord between the overlapped layers of the aponeurosis of the external oblique muscle.

Type 4: Repairs with transplantation of the cord external to the aponeurosis of the external oblique muscle, with or without overlapping of the aponeurosis.

Type 4A: Same as type 4, with suture of the conjoined tendon to the inguinal ligament with a fascial suture from the aponeurosis of the external oblique muscle.

Type 4B: Same as type 4, with suture of the conjoined tendon to the inguinal ligament with a fascial suture obtained from the fascia lata.

Type 5: Repairs in which the rectus muscle or the anterior rectus sheath was sutured to the inguinal ligament.

Type 6: Repairs in which the testicle and cord were brought down through the femoral opening and into the scrotum.

† The percentages of infections were calculated on the entire number of repairs in each group. The percentages of infected wounds showing recurrences were calculated according to the number of recurrences found among the total infected wounds which were examined in the follow-up clinic for nine months or longer.

With both types of hernias the two groups, "without fascial sutures" and "with fascial sutures," are large enough for comparative recurrence figures to be obtained. With both types of recurrent hernias the results were favorable to the use of fascial sutures in the repair of these hernias. This difference is particularly outstanding when one considers that in the majority of instances catgut alone was used in the less difficult repairs and fascial sutures in those presenting the greater obstacles to the performance of a satisfactory repair.

TABLE 20.—*Direct Inguinal Recurrences: Type of Repair*

Type of Repair *	Total Followed	Per Cent Recurrences	Per Cent Infections †	Per Cent Infections Showing Recurrences †	Per Cent Recurrences	
					Indirect	Direct
(A)						
1	4	0.0	0.0	...	....	.....
2	23	34.7	0.0	...	0.0	100.0
2A	6	16.7	16.7	0.0	0.0	100.0
2B	26	11.5	3.8	100.0	0.0	100.0
3	3	66.7	0.0	...	0.0	100.0
4	16	37.5	6.3	0.0	16.7	83.3
4A	5	20.0	20.0	0.0	0.0	100.0
4B	7	14.3	0.0	...	0.0	100.0
5	25	24.0	4.0	0.0	16.7	83.3
Totals	115	24.4	3.6	14.3	7.1	92.9
(B)						
All repairs without fascial sutures	71	31.0	2.8	0.0		
All repairs with fascial sutures	44	13.6	6.8	20.0		
Totals	115	24.4	3.6	14.3		

* Type 1: Repairs without transplantation of the cord.

Type 2: Repairs with transplantation of the cord between the conjoined tendon and the aponeurosis of the external oblique muscle.

Type 2A: Same as type 2, with suture of the conjoined tendon and the inguinal ligament with a fascial suture obtained from the aponeurosis of the external oblique muscle.

Type 2B: Same as type 2, with suture of the conjoined tendon to the inguinal ligament with a fascial suture obtained from the fascia lata.

Type 3: Repairs with transplantation of the cord between the overlapped layers of the aponeurosis of the external oblique muscle.

Type 4: Repairs with transplantation of the cord external to the aponeurosis of the external oblique muscle, with or without overlapping of the aponeurosis.

Type 4A: Same as type 4, with suture of the conjoined tendon to the inguinal ligament with a fascial suture obtained from the aponeurosis of the external oblique muscle.

Type 4B: Same as type 4, with suture of the conjoined tendon to the inguinal ligament with a fascial suture obtained from the fascia lata.

Type 5: Repairs in which the rectus muscle or the anterior rectus sheath was sutured to the inguinal ligament.

† The percentages of infections were calculated on the entire number of repairs in each group. The percentages of infected wounds showing recurrences were calculated according to the number of recurrences found among the total infected wounds in each group which were examined in the follow-up clinic for nine months or longer.

TABLE 21.—*Indirect Inguinal Recurrences: Postoperative Complications*

Complication	Total Operations	Per Cent of Entire Group	Average Post-Operative Stay in Hospital, Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1. Acute bronchitis	13	10.2	17.8	11	1	9.1	0.0	0	0.0
2. Wound infection	9	7.0	19.0	6	0	0.0	...	0	0.0
3. Hematomas	3	2.3	20.0	2	0	0.0	0.0	0	0.0
4. Pulmonary embolus	2	1.6	46.0	2	0	0.0	0.0	0	0.0
5. Acute otitis media	1	0.8	13.0	1	0	0.0	0.0	0	0.0
6. Empyema	1	0.8	55.0	1	0	0.0	0.0	0	0.0
7. Central pneumonia	1	0.8	18.0	1	0	0.0	0.0	0	0.0
8. Prostatic abscess	1	0.8	25.0	0	..	...	0.0	0	0.0
9. Hiccups	1	0.8	19.0	1	0	0.0	0.0	0	0.0
Totals	32	25.0		25	1	4.0	0.0*	0	0.0

* Excluding those patients whose only complication was wound infection.

TABLE 22.—*Direct Inguinal Recurrences: Postoperative Complications*

Complication	Total Operations	Per Cent of Entire Group	Average Post-Operative Stay in Hospital, Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1. Acute bronchitis	8	5.7	17.4	7	3	42.9	12.5	0	0.0
2. Wound infection	5	3.6	20.2	3	1	33.3	...	0	0.0
3. Broncho-pneumonia	4	2.9	18.5	3	1	33.3	0.0	1	25.0
4. Hematomas	3	2.1	17.3	3	0	0.0	0.0	0	0.0
5. Lobar pneumonia	1	0.7	18.0	1	0	0.0	0.0	0	0.0
6. Coronary occlusion	1	0.7	6.0	..	..	...	0.0	1	100.0
7. Pyelitis	1	0.7	20.0	0	..	...	0.0	0	0.0
Totals....	23	16.4		17	5	29.5	5.8*	2	8.7

* Excluding those patients whose only complication was wound infection.

TABLE 23.—*Indirect Inguinal Recurrences: Respiratory Postoperative Complications*

Complication	Total Operations	Per Cent of Entire Group	Average Post-Operative Stay in Hospital, Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1. Acute bronchitis	13	10.2	17.8	11	1	9.1	0.0	0	0.0
2. Pulmonary embolus	2	1.6	46.0	2	0	0.0	0.0	0	0.0
3. Acute otitis media	1	0.8	13.0	1	0	0.0	0.0	0	0.0
4. Empyema	1	0.8	55.0	1	0	0.0	0.0	0	0.0
5. Central pneumonia	1	0.8	18.0	1	0	0.0	0.0	0	0.0
Totals....	18	14.1		16	1	6.3	0.0	0	0.0

TABLE 24.—*Direct Inguinal Recurrences: Respiratory Postoperative Complications*

Complication	Total Operations	Per Cent of Entire Group	Average Post-Operative Stay in Hospital, Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1. Acute bronchitis	8	5.7	17.4	7	3	42.9	12.5	0	0.0
2. Broncho-pneumonia	4	2.9	18.5	3	1	33.3	0.0	1	25.0
3. Lobar pneumonia	1	0.7	18.0	1	0	0.0	0.0	0	0.0
Totals....	13	9.3		11	4	36.4	7.7	1	7.7

Recurrences followed 14.8 per cent of the repairs of indirect inguinal recurrent hernias done with catgut alone and only 5.9 per cent when a fascial suture was used. However, four times as many wound infections developed after the use of the latter, 17.6 per cent, than when catgut suture material alone was employed, 4.9 per cent. However, none of the infections in either instance was followed by recurrence of the hernia.

In the case of repairs of direct inguinal recurrences, a second recurrence appeared after the use of catgut alone in 31 per cent, and this happened in only 13.6 per cent when fascial sutures were used. This

TABLE 25.—*Indirect Inguinal Recurrences: Circulatory Postoperative Complications*

Complication	Total Operations	Per Cent of Entire Group	Average Post-Operative Stay in Hospital, Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1. Hematomas	3	2.3	20.0	2	0	0.0	0.0	0	0.0
2. Pulmonary embolus	2	1.6	46.0	2	0	0.0	0.0	0	0.0
Totals....	5	3.9		4	0	0.0	0.0	0	0.0

TABLE 26.—*Direct Inguinal Recurrences: Circulatory Postoperative Complications*

Complication	Total Operations	Per Cent of Entire Group	Average Post-Operative Stay in Hospital, Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1. Hematomas	3	2.1	17.3	3	0	0.0	0.0	0	0.0
2. Coronary occlusion	1	0.7	6.0	..	..	...	0.0	1	100.0
Totals....	4	2.8		3	0	0.0	0.0	1	25.0

held true even though the incidence of infected wounds was increased from 2.8 per cent to 6.8 per cent, and 20 per cent of the patients with infected wounds in which fascial sutures were employed had a recurrence later.

POSTOPERATIVE COMPLICATIONS

Indirect Inguinal Recurrences.—Postoperative complications followed 25 per cent of the repairs of indirect inguinal recurrences. This was two and one-half times as great an incidence as followed the primary repairs of incomplete indirect inguinal hernias. However, none of these complications caused the death of a patient. Acute bronchitis was the only complication followed by a recurrence, and for the group of repairs fol-

lowed by some postoperative complication the recurrence rate was only 9.1 per cent, as compared with 11.6 per cent for all repairs of indirect inguinal recurrences.

Respiratory complications followed 14.1 per cent, as compared with 7.3 per cent of the primary repairs. The increase in the incidence of circulatory complications was less marked, 3.9 per cent as compared with 2.8 per cent. Wound infection developed in 7 per cent, as compared with 3.5 per cent in the repairs of the primary incomplete indirect inguinal hernias.

Direct Inguinal Recurrences.—The increased incidence of postoperative complications found in the group of hernias just under discussion was not observed in repairs of direct inguinal recurrences. The figures were: repairs of recurrences, 16.4 per cent, and primary repairs, 21.1 per cent. Bronchopneumonia and coronary occlusion were each the cause of 1 death.

TABLE 27.—*Direct Inguinal Recurrences: Deaths (1926-1935)*

Operative Deaths *	Patient's Age	Hernia Strangulated	Duration of Strangulation	Resection Required	Time of Death (Postoperative)	Cause of Death
1.	48	No	..	..	20 days	Bronchopneumonia
2.	50	No	..	..	6 days	Coronary occlusion

* Two deaths in 87 operations, giving an operative mortality of 2.3 per cent.
Two patients died who were not operated on. They were moribund when admitted with strangulated hernias, one of 8 days' duration and the other of 3 weeks' duration. One patient was 60 and the other 68 years of age.

Respiratory complications followed 9.3 per cent of repairs of the direct recurrences, as compared with 13.3 per cent of the primary repairs, and the figures for circulatory complications were 2.8 and 3 per cent respectively.

The main complications in the two groups of repairs appeared in the same sequence.

OPERATIVE MORTALITY

No deaths followed the 86 repairs of indirect inguinal recurrences performed in the ten year period from 1926 to 1935 inclusive.

Two deaths followed the 87 repairs of direct inguinal recurrences done in the ten year period 1926 to 1935. One patient, 50 years of age, died on the sixth postoperative day owing to a coronary occlusion. The other was 48 years of age and died of bronchopneumonia on the twentieth postoperative day. Neither of the two hernias had been strangulated.

One patient, aged 60 years, entered the hospital moribund, with a strangulation of three weeks' standing. She died immediately after admission, no attempt having been made to repair the hernia. The same was true of another patient, 68 years of age, with a strangulation present eight days before admission to the hospital.

FOLLOW-UP DATA

Indirect Inguinal Recurrences.—In this group 128 hernias were studied, all of which were repaired. Twenty-two patients did not return for follow-up examination. Eleven were observed postoperatively for less than nine months without a recurrence having been discovered. Ninety-five patients were followed for nine months or longer or were found to have a recurrence within less than nine months.

TABLE 28.—*Indirect Inguinal Recurrences: Follow-Up Data*

Total number of hernias studied	128	
Total with no operation	0	
Total operations	128	
Total operative deaths	0	
Total with no follow-up examination	22	
Total with follow-up under 9 months (no recurrence)	11	
Total with follow-up 9 months and over (including recurrences)	95	
Average follow-up time (all cases followed 9 months and over)	36	months
Total recurrences	11	
Average postoperative time recurrences were first noted	18.5	months
Percentage of recurrences (follow-up 9 months and over)	11.6	
Total number of operations examined postoperatively	106	
Average follow-up time (all followed cases)	32.1	months
Total recurrences	11	
Percentage of recurrences (all followed cases)	10.5	

Recurrences: indirect, 9.1%; direct, 90.9%.

TABLE 29.—*Direct Inguinal Recurrences: Follow-Up Data*

Total number of hernias studied	154	
Total with no operation	14	
Total nonoperative deaths	2	
Total operations	140	
Total operative deaths	2	
Total with no follow-up examination	15	
Total with follow-up under 9 months (no recurrences)	10	
Total with follow-up 9 months and over (including recurrences)	115	
Average follow-up time (all cases followed 9 months and over)	40.4	months
Total recurrences	28	
Average postoperative time recurrences were first noted	20.6	months
Percentage of recurrences (follow-up 9 months and over)	24.4	
Total number of operations examined postoperatively	125	
Average follow-up time (all followed cases)	37.5	months
Total recurrences	28	
Percentage of recurrences (all followed cases)	22.4	

Recurrences: indirect, 7.1%; direct, 92.9%.

The average length of time over which all followed cases were observed was thirty-two and one-tenth months. The 11 discovered recurrences gave a recurrence rate of 10.5 per cent. The average follow-up period for those followed nine months or more was thirty-six months. Of this group of 95 repairs, recurrences developed in 11, or 11.6 per cent. The average time postoperatively at which the recurrences were first noted was eighteen and one-half months.

Of the 11 recurrences, 90.9 per cent were direct and 9.1 per cent indirect, as compared with 60 per cent direct and 40 per cent indirect after primary repairs of incomplete indirect inguinal hernias.

Direct Inguinal Recurrences.—Of the 154 direct inguinal recurrences studied, 14 were not repaired. Among the 140 patients on whom repairs were performed, 2 died postoperatively, and 15 did not return for follow-up examination. Ten repairs were observed for less than nine months without a recurrence having been discovered. A total of 115 repairs were followed postoperatively for nine months or longer or until a recurrence was noted.

TABLE 30.—*Indirect Inguinal Recurrences: Sequence of Recurrences When Known*

Type of Original Hernia	Type of Original Operation	Type of Repaired Recurrence	Type of Repair	Type of Present Recurrence	Interval Before Recurrence
Direct	.....	Indirect	Halsted	Direct	2 weeks
Direct	.....	Indirect	Halsted	Direct	6 months
.....	.....	Indirect	Bassini-Gallie	Direct	6 months
.....	.....	Indirect	Halsted	Direct	8 months
Indirect *	.....	Indirect	Willys-Andrews	Direct	12 months
Indirect *	.....	Indirect	Bassini	Direct	13 months
Indirect *	Bassini	Indirect	Ferguson	Direct	13 months
Complete indirect	Ferguson	Indirect	Bassini	Direct	16 months
.....	.....	Indirect	Bassini	Direct	18 months
Indirect *	.....	Indirect	Bassini-McArthur	Direct	2½ years
Indirect *	Bassini	Indirect	Bassini	Indirect	8½ years

* Hernias listed as indirect without qualification were all incomplete indirect hernias.

The average time covered by the follow-up for the 125 repairs observed postoperatively was thirty-seven and one-half months, and the recurrence rate was 22.4 per cent. For the 115 repairs observed for nine months or longer or until a recurrence was noted, the average follow-up time was forty and four-tenths months, and the recurrence rate was 24.4 per cent. The 28 recurrences were discovered after an average postoperative interval of twenty and six-tenths months.

The proportion of direct and indirect recurrences which followed the repair of direct inguinal recurrences was essentially the same as for the primary repairs: 92.9 per cent direct and 7.1 per cent indirect for the former and 90.9 per cent direct and 9.1 per cent indirect for the latter.

SEQUENCE OF RECURRENCES

The sequences of the types of operations and recurrences, when known, are presented in tables 30 and 31. The data in these tables are of considerable interest, but the number of cases in which the information was complete was too small to be of value in drawing conclusions.

REPAIR OF RECURRENT INGUINAL HERNIAS

Various significant points regarding the repair of indirect and of direct recurrent inguinal hernias may be discussed together, as the recurrences following repairs of these two types of hernias appear as direct

TABLE 31.—*Direct Inguinal Recurrences: Sequence of Recurrences When Known*

Type of Original Hernia	Type of Original Operation	Type of Repaired Recurrence	Type of Repair	Type of Present Recurrence	Interval Before Recurrence
Indirect *	Anatomic	Direct	Rectus transplant	Direct	1 month
Indirect *	Rectus transplant	Direct	Halsted	Direct	1 month
Direct	Bassini	Direct	Rectus transplant	Direct	1 month
.....	.....	Direct	Bassini	Direct	2 months
Indirect *	Bassini	Direct	Willys-Andrews	Direct	2 months
.....	.....	Direct	Rectus transplant	Direct	3 months
.....	.....	Direct	Rectus transplant	Direct	4 months
.....	.....	Direct	Bassini	Direct	4 months
.....	.....	Direct	Rectus transplant	Indirect	6 months
Direct	Bassini	Direct	Bassini-Gallie	Direct	6 months
.....	.....	Direct	Halsted	Direct	7 months
.....	.....	Direct	Bassini	Direct	8 months
.....	.....	Direct	Halsted	Indirect	8 months
.....	.....	Direct	Bassini-Gallie	Direct	8 months
Direct	Halsted	Direct	Willys-Andrews	Direct	8 months
.....	.....	Direct	Bassini	Direct	9 months
.....	.....	Direct	Bassini	Direct	10 months
.....	.....	Direct	Bassini	Direct	11 months
Direct	Halsted-McArthur	Direct	Halsted-Gallie	Direct	12 months
Direct	Bassini	Direct	Bassini	Direct	13 months
.....	.....	Direct	Halsted	Direct	21 months
.....	.....	Direct	Halsted	Direct	19 months
.....	.....	Direct	Bassini-Gallie	Direct	2 years
.....	.....	Direct	Bassini-McArthur	Direct	2 years, 2 months
Direct	Rectus transplant	Direct	Rectus transplant	Direct	3 years
.....	.....	Direct	Bassini	Direct	3 years, 9 months
.....	.....	Direct	Halsted-McArthur	Direct	10 years
Indirect *	Halsted	Direct	Halsted	Direct	11 years, 6 months

* These 4 indirect inguinal hernias were incomplete.

or indirect in essentially the same proportions, being predominantly direct in both instances.

Consequently, in the repair of either of these two types of recurrent inguinal hernia, reconstruction of the floor of the inguinal canal is of primary importance. Careful imbrication of the transversalis fascia, thereby approximating the inferior edge of the conjoined tendon to the

inguinal ligament, appears to be the logical first step in these repairs. This maneuver prevents the insinuation of pieces of properitoneal fat between the later approximated edges of the conjoined tendon and inguinal ligament.

If the groups of followed cases in this study can be considered sufficiently large for the resultant recurrence rates to be accurate, the conclusion must be drawn that these recurrent inguinal hernias should be repaired by the use of a fascial suture. Several authors have in the past few years advocated the substitution of silk suture technic for the use of fascial sutures. To date at St. Luke's Hospital there are no records of sufficiently large groups of repairs with adequately long follow-up periods to enable one to draw any conclusions in this matter. However, until greater numbers of followed cases in whose repairs silk sutures were used exclusively without selection of cases are available for study, I am of the opinion that the majority of the recurrent inguinal hernias should be repaired with either the McArthur or the Gallie technic, silk being used throughout for sutures, ligatures and fixation of the fascial sutures.

Points as to the general technic of dissection and repair of these hernias are the same as in the repair of the primary inguinal hernias. Among these are careful, clean dissection, maintenance of hemostasis and asepsis, care that sutures are not tied too tightly, inclusion of bleeding vessels only without adjacent tissues in the ligatures and reduction of the size of the cord when necessary at its point of exit through the internal ring.

1213 Medical Arts Building.

CHANGES IN BONES AND JOINTS RESULTING FROM INTERRUPTION OF CIRCULATION

II. NONTRAUMATIC LESIONS IN ADULTS WITH BONE INFARCTION; ARTHRITIS DEFORMANS

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The recognized causes of interruption of the circulation and infarction of the viscera are embolism, thrombosis, arteriosclerosis and obliterative endarteritis. In case of gangrene of the extremities neurogenic vascular spasm (Raynaud's disease) and ergot intoxication must be added to this list. In view of the relative frequency of these circulatory disturbances in adults, it is surprising that similar lesions of bones have not been more frequently reported to accompany them. As was brought out under general considerations in part I of this study, most of the lesions resulting from nontraumatic interruption of circulation of bone in adults that have heretofore been described have not definitely been traced to the aforementioned causes and with some of the lesions to be described here there is much uncertainty either as to the cause or as to the exact mechanism of action of the exciting factor. That arteriosclerosis, obliterative endarteritis and neurogenic and toxic vascular changes may be potential or contributory factors by creating so-called functional end arteries in regions of bone where true end arteries are not normally found is to be borne in mind in attempting an explanation of bone infarction in adults.

CAISSON DISEASE

It has long been known that caisson disease is due to damage of the tissues by nitrogen, which, having been absorbed in excess by the body under compression, forms bubbles in the tissues and body fluids from too rapid decompression. The nitrogen within the blood vessels produces embolism of the viscera with varying effects, sometimes causing death. Fat and lipoids absorb much greater quantities of nitrogen than do other tissues and body fluids, accounting for the frequent damage and mottling of the subcutaneous tissues. Nitrogen frequently accumulates in bubbles within the spinal cord, where it is liberated from the high lipoid content of cord tissue and results in varying degrees of paralysis, especially in

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the lower extremities. Bassoe [1] and Bornstein [2] were the first to report a deforming type of arthritis in the hips and shoulders as a sequel of caisson disease, and Bassoe described blotchy roentgen shadows of increased density within the shaft of the tibia in 2 cases. Numerous cases in which articular changes occurred have since been reported, as will be seen by consulting the bibliographies of three of the articles cited.[3]

Kahlstrom, Burton and I [3a] reported 4 cases of caisson disease of long standing in which there were bone infarcts, some in the shafts and some in the epiphyses of the long bones, which because of either calcification of their walls or collapse or sequestration from weight bearing were recognizable in roentgenograms. In 3 of the cases there were the changes associated with deforming arthritis, some of which were in the hips and some in the shoulders. The diagnosis was confirmed by necropsy in 1 case and by biopsy in another. Since then the diagnosis in case 4 of the series has been confirmed by a surgical excision, which will be discussed later. The massive bone necrosis was attributed to the liberated nitrogen, but uncertainty was expressed as to the exact method of action. In favor of infarction from nitrogen embolism were the extensive involvement of the diaphysis or of the epiphysis with freedom from involvement of the other and predilection for the head of the femur, which is known to be the most frequent seat of end arteries in the adult skeleton. But against nitrogen embolism is the fact that the infarcts were very extensive and that the extensive embolism of viscera which might be expected to accompany such an amount of bone embolism would be likely to cause death. Since the involved bones were limited to the extremities, since the bones of the extremities are rich in fatty marrow and since fat absorbs relatively a very large amount of nitrogen, a plausible theory is that nitrogen bubbles liberated within the medullary canals, where absorption is slow, kill the tissues by direct compression. When the epiphysis is involved and the necrotic bone borders on the joint, the overlying articular cartilage undergoes either extensive or complete necrosis. Use of the limbs in the presence of the necrosis may cause the head of the femur or of the

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1. Bassoe, P.: Compressed Air Disease, J. Nerv. & Ment. Dis. **38**:368, 1911; The Late Manifestations of Compressed Air Disease, Am. J. M. Sc. **145**:526, 1913.

2. Bornstein, A.: Versuche ueber die Prophylaxe der Pressluftkrankheit, Berl. klin. Wchnschr. **47**:1272, 1910.

3. (*a*) Kahlstrom, S. C.; Burton, C. C., and Phemister, D. B.: Aseptic Necrosis of Bone: I. Infarction of Bones in Caisson Disease Resulting in Encapsulated and Calcified Areas in Diaphyses and in Arthritis Deformans, Surg., Gynec. & Obst. **68**:129, 1939; II. Infarction of Bones of Undetermined Etiology Resulting in Encapsulated and Calcified Areas in Diaphyses and in Arthritis Deformans, ibid. **68**:631, 1939. (*b*) Coley, B. L., and Moore, M., Jr.: Caisson Disease with Special Reference to the Bones and Joints: Report of Two Cases, Ann. Surg. **111**:1065, 1940. (*c*) Ugolotti, F.: La forma osteoarticulare della malättia dei cassoni e sua interpretazione medico-legale, Assistenze sociale **14**:xviii, 1940.

humerus to collapse, which may greatly deform the joint. Chronic deforming arthritis is a relatively late sequel, its development being secondary to the necrosis of the articular cartilage as first described in association with other conditions by Axhausen.[4] Coley and Moore [3b] have since reported 2 cases of caisson disease with pain and stiffness of long standing in the shoulder and hip joints in which roentgenograms demon-

Fig. 1 (case 1).—Caisson disease of three years' duration, producing necrosis in the head of the femur and collapse of the weight-bearing articular surface (x).

strated not only chronic deforming arthritis but large to small circumscribed areas of increased density in the shafts and epiphyses, indicative of bone infarcts. Ugolotti [3c] has recently reported a case of caisson disease in which at the end of twenty months mottled areas of increased

4. Axhausen, G.: Arthritis deformans und ihre Abarten, Arch. f. klin. Chir. **126**:573, 1923.

and decreased density in the head, neck and trochanteric regions of the femurs and of the head and surgical neck of the left humerus, interpreted as infarcts, were visible in roentgenograms.

In the following case of caisson disease there was necrosis of the head of the femur with collapse of the weight-bearing portion, but roentgen signs of chronic arthritis were not yet visible.

CASE 1.—A. C., a man aged 51 years, was seen April 22, 1940. Three years previously the patient, who worked at tunnel construction under 35 pounds (15.9 Kg.) of compressed air, noticed severe pains in the lower limbs about two hours after leaving the compression chamber. Return to the decompression lock did not give relief. The pains continued, and he was confined to bed for three weeks. He then returned to light work but has since continued to have pains in the hips, much more marked in the right than in the left, with extension down the right leg. The right hip is at present lame and weak.

Physical examination revealed him to be large and muscular. He had a slight limp referable to the right hip. There were moderate limitation of rotation and abduction of the right hip joint, but flexion was only slightly limited. Physical examination otherwise showed him to be essentially normal. A roentgenogram (fig. 1) of the right hip showed a break in the shadow of the articular cortex underlying the superior acetabular margin (*x*), with a moderate depression of the weight-bearing portion of the head, extending mesially to the region of the acetabulum. There were mottling and streaking of the shadow of the underlying head and an irregular zone of increased density in the adjacent border of the neck and laterally in the noncollapsed portion of the head. The diagnosis of necrosis of the head followed by collapse of the weight-bearing portion was based on the similarity of the roentgenograms to those in proved cases of necrosis and collapse of the head produced by caisson disease, fracture of the neck of the femur and dislocation of the hip. The changes of chronic deforming arthritis had not yet begun. Roentgenograms of the rest of the body showed a normal bone and joint picture.

Pathologic studies of one shoulder and both hip joints obtained at autopsy in case 1 of the series reported by Kahlstrom, Burton and me (the condition was of thirty-five years' standing) revealed the final stages of such articular changes. There were flattening of the heads of the bones, replacement of articular cartilage by irregularly thinned fibrocartilage, marked lipping of the articular margins, osteocartilaginous loose bodies in the joints, medium to slight chronic villous synovitis, subcortical bony cavities in the heads filled with fibrous tissue or fluid and irregularly arranged living bone which had replaced the old dead bone of the heads.

Resection of the head of the right femur in case 4 of the same series has since given opportunity for pathologic study of the disease in a less advanced stage than that aforementioned. At the time of the original report the disease was of twenty-one years' standing. There was roentgen evidence of flattening and mottled increase in density in the heads of the femurs and humeri, of marginal lipping of their joints and of

faintly walled-off and calcified infarcts in the shafts of the femurs and the tibias. One year later the patient (case 2 of this series, not reported in detail here) was having great difficulty with the hips in walking. Roentgenograms revealed little or no advance in the lesions of the bones and joints. In figure 2 (the right hip) evidence of marked lipping, irregularity of the weight-bearing portion of articular surface of the head and blotchiness of underlying bone were observed. The major por-

Fig. 2 (case 2).—Caisson disease of the right hip of twenty-two years' duration.

tion of the head was then resected in an attempt to improve the function of the hip. Marginal osteophytes and moderate villous arthritis were present. Figure 3 is a photograph of a coronal section of the more or less fragmented resected portion. The articular surface of the weight-bearing portion was flattened, and its cartilage was thin and irregular. At one point (x), there was a dense sequestrated pea-sized piece of cortical bone and articular cartilage. Figure 4 shows a microscopic section of the head. The bone of the interior was irregularly arranged as if reconstructed and viable. The lateral, nonweight-bearing portion of

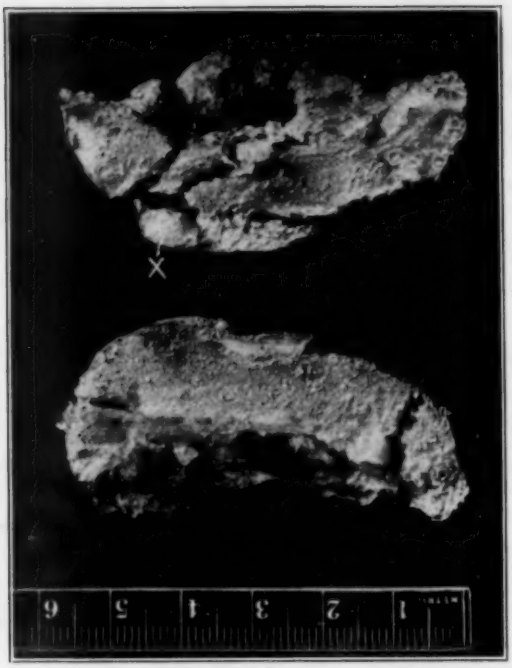

Fig. 3 (case 2).—The two halves of a coronal section of the resected head showing a deformed articular surface and a sequestrum (*x*) bordering on the joint.

Fig. 4 (case 2).—Microscopic section of the head, showing the lateral non-weight-bearing surface (*x*) not collapsed and the weight-bearing surface at the top and mesially (*y*) irregular and collapsed.

Fig. 5 (case 2).—Section of a sequestrum (*x*, fig. 3) from the articular surface. The cartilage and bone are dead.

the head was covered by a thick layer of fibrocartilage (x). The top of the head had been destroyed, leaving a broad groove partly filled by fibrous tissue which surrounded some dead bony trabeculae. Mesial to this there was a thin irregular covering of fibrocartilage. The loose

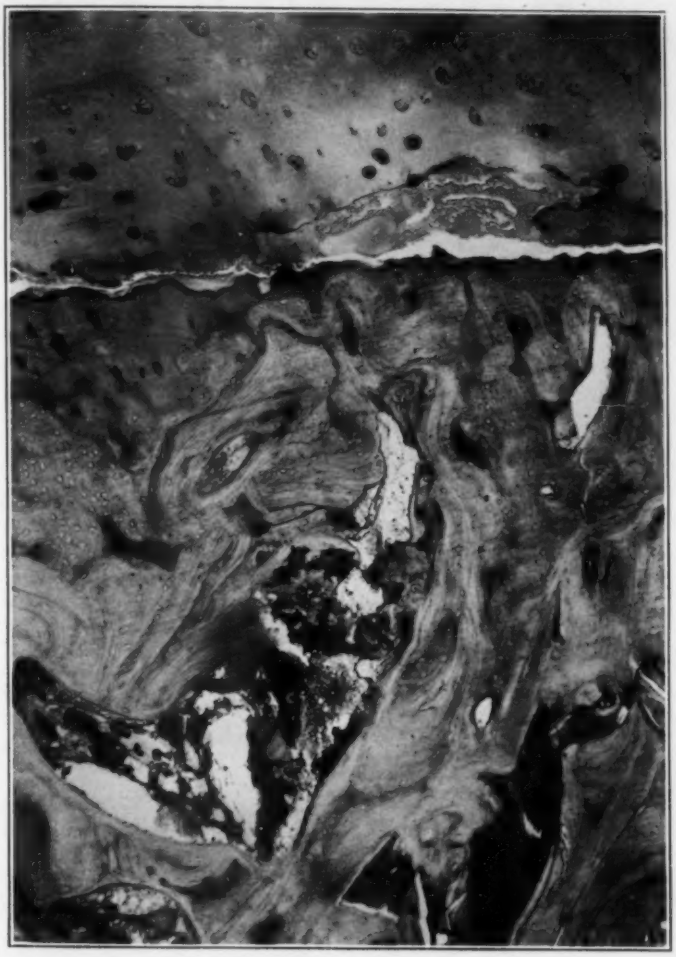

Fig. 6.—High power view of the section shown in figure 5. Note the dead cartilage and bone, with calcareous deposits in the spaces.

piece of cortex (x) of figure 3 was sectioned. It was found to consist of old dead articular cartilage and underlying bone similar to a loose body in a case of osteochondritis dissecans (fig. 5). On microscopic examination (fig. 6) the bony lacunae were seen to be empty; the marrow spaces were partly filled with calcareous deposits, and the cartilage was partly detached from the bone. This was a portion of the

necrotic head which in the region of greatest weight bearing became detached, remained separate and consequently did not undergo creeping replacement by new bone and fibrocartilage as was the case in the rest of the head.

When the necrotic area is located in a diaphysis or in an epiphysis away from the articular cortex, it is invaded by blood vessels and osteo-

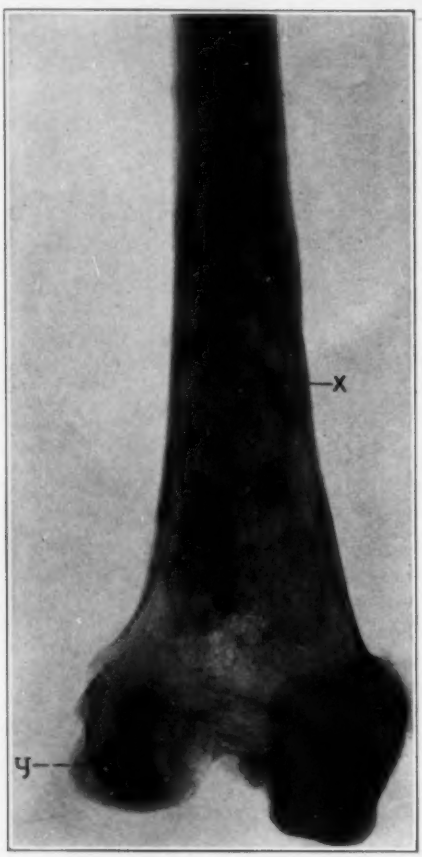

Fig. 7.—Caisson disease of thirty-five years' duration. Note the old infarcts with a calcified zone of demarcation in the shaft (x) and in the epiphysis (y).

genic elements at its periphery and is gradually reduced in size through creeping substitution by new bone. Smaller infarcts may be in the course of months or years completely replaced by new bone, but in the case of large ones, especially of the shafts, the replacement process comes to a standstill and the remaining necrotic bone becomes walled off by fibrous tissue, which eventually calcifies and ossifies, giving a sharp line of demarcation. The interior may also become calcified in

part, so that after a long time the infarct casts a characteristically dense circumscribed shadow in roentgenograms. Figure 7 is a roentgenogram of the lower half of the necropsy specimen of the right femur in case 1 in the series reported by Kahlstrom, Burton and me. It shows a massive dense infarct in the shaft and a small one in the lateral condyle thirty-five years after the attack of caisson disease. It should be emphasized that roentgenograms taken in the early stages and even after the lapse of a few years may show no shadow outlining the infarct because calcification has not yet set in. A biopsy in case 2 of the aforementioned series, in which the disease was of four years' duration, showed no calcification of the dead bone in the head of the femur. Dr. C. Howard Hatcher, of this department, has produced caisson disease experimentally in dogs, but in no instance was bone infarction found.

ARTERIOSCLEROSIS AND BONE INFARCTION

In the following case of old calcified infarct of the tibia there was marked generalized arteriosclerosis which led to a fatal termination. While there was no direct proof that arteriosclerosis was the cause of the infarction, it appeared to be the most plausible explanation.

CASE 3.—A white man aged 52 years consulted Dr. C. C. Burton, who has supplied the following history and permitted study of the involved bone. Four months before coming under Dr. Burton's care (Feb. 14, 1938), the patient fell and fractured the medial condyle of the right femur. Weight extension was applied to a Steinmann pin through the os calcis, but extensive osteomyelitis developed and was still active on admission.

The past history revealed a normal childhood and adolescence. The patient began work as a coal miner and continued in that occupation for twenty-two years. Then he served in the army during the World War, as an automobile factory worker for eight years and as a janitor up to the date of injury. He never worked in compressed air and never had symptoms of bends or pains in the extremities or in any of the joints.

Physical examination showed him to be well developed. The blood pressure was 100 systolic and 60 diastolic. The Wassermann and Kahn reactions were negative. The urine was within physiologic limits. Regional examination revealed no abnormality except in the right lower extremity. The right knee showed increased lateral mobility. The right ankle was markedly stiff, swollen, tender and tense. There was a sinus discharging pus beneath the external malleolus.

Roentgenograms of the foot and ankle revealed osteomyelitis with marked destruction of the os calcis and osteoporosis of the other bones of the foot and ankle. Roentgenograms of the femur showed a healed fracture of the medial condyle. Roentgenograms of the upper end of the right tibia revealed an area of blotchy increased density situated centrally in the upper 2½ inches (7.2 cm.) of the diaphysis, measuring approximately 1 inch (2.5 cm.) in diameter above and tapering slightly downward to the lower end. A bone infarct was diagnosed and roentgenograms were then made of the rest of the bones of the extremities, but no abnormalities were revealed

The right leg was amputated 6 inches (15 cm.) below the knee because of the osteomyelitis. The patient later wore an artificial limb but did not return to work

He died suddenly one year and ten months after the operation. The peripheral arteries were noticeably sclerotic. The pleural and peritoneal spaces were clear and free from fluid. There were old healed fractures of the right seventh and eighth ribs. The heart weighed 300 Gm. There were marked arteriosclerosis, calcification and narrowing of the coronary arteries. No gross infarction of the myocardium or valvular disease was observed.

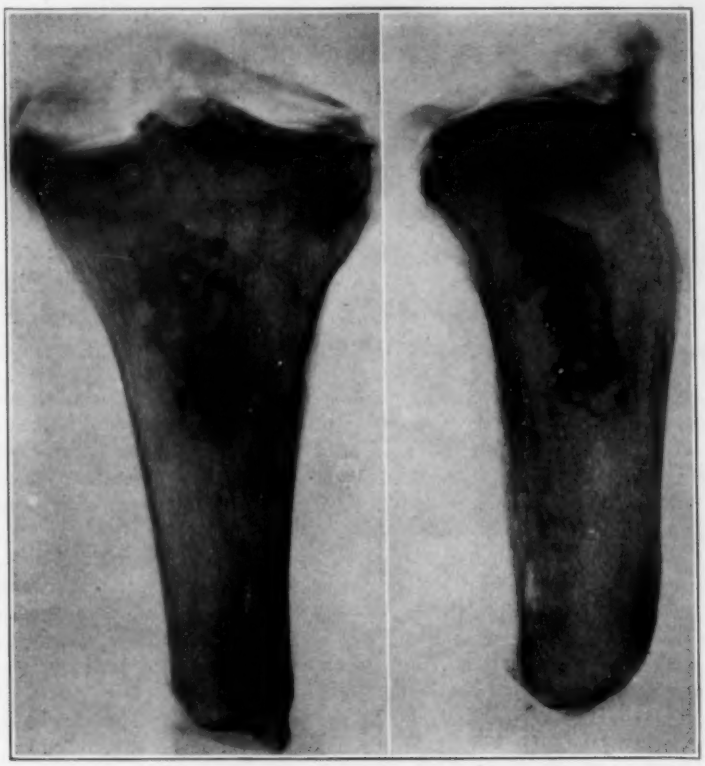

Fig. 8 (case 3).—Roentgenograms of the stump of the tibia obtained at autopsy, showing an old infarct of the diaphysis.

The entire aorta was atheromatous, with discolored subintimal areas, probably due to hemorrhage. The lungs, liver, spleen and kidneys showed pronounced passive congestion but no evidence of infarcts, recent or old. There were petechial hemorrhages in the spleen and in the pancreas.

Microscopic examination revealed marked generalized arteriosclerosis, coronary arteriosclerosis, degeneration and fatty infiltration of the myocardium and passive congestion of all of the viscera, but no signs of infarcts. The immediate cause of death was heart failure.

The stump of the right tibia was sent for pathologic study. The lower end was rounded and covered by a thick layer of fibrous tissue. The synovial lining

of the knee was slightly villous in places and was stained brown from blood pigment derived from the old fracture of the femur into the joint. The articular and semilunar cartilages showed no gross abnormalities. Roentgenograms were made of the specimen (fig. 8). When these were compared with those of the upper end of the tibia taken twenty months previously, just before amputation of the leg was performed, no change in appearance was detected. The central area of increased density in the upper portion of the diaphysis appeared blotchy in the anteroposterior view, but in the lateral view its central portion was unevenly radiolucent, while the periphery was somewhat circinate in arrangement

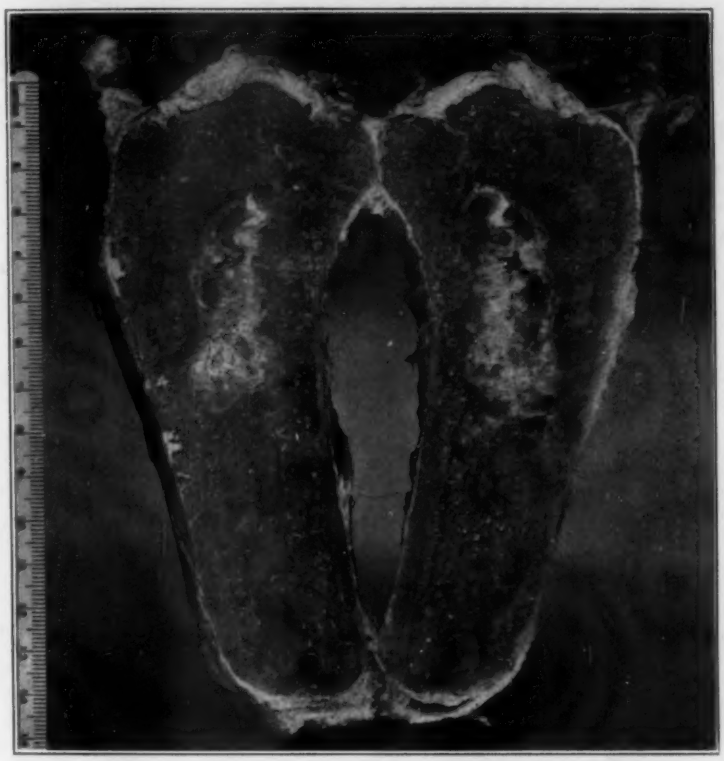

Fig. 9 (case 3).—Sagittal section of the amputation stump.

and was radiopaque. The shadows of bony trabeculae in most of the area for short distances about were irregularly arranged as if representing new bone which had replaced the old bone. The rest of the bone was reduced in density.

A sagittal section (fig. 9) revealed a thin cortex, fine cancellous bone and much fatty gelatinous marrow, indicative of atrophy of disuse. In the center of the upper diaphysis was a mottled, irregularly outlined, grayish to light yellow area approximately 5.5 cm. long by 1 to 2 cm. broad. In its upper portion there was a dark necrotic central area; about this and extending downward was a yellowish calcified area, and external to this was an irregular layer of grayish fibrous tissue. A slice was cut through the involved area, of which a roentgenogram was made (fig. 10*A*). The slice was then decalcified and a microscopic

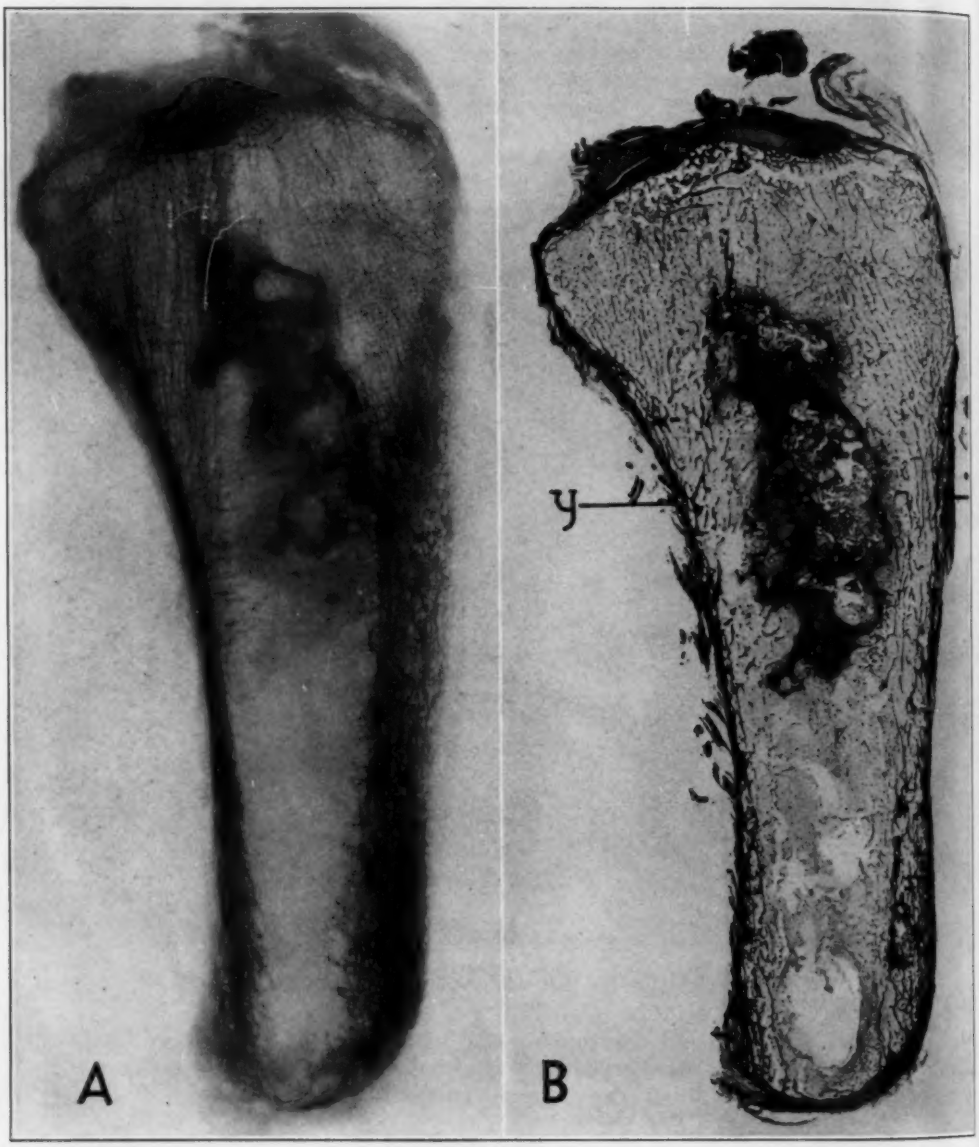

Fig. 10 (case 3).—*A*, roentgenogram of a slice of the tibial stump, showing dense shadows cast by the infarct. *B*, microscopic section of the stump, showing the infarct.

section prepared (fig. 10 *B*). The central necrotic areas, the calcified intermediary zone and the outer fibrous zone of the involved area and the atrophic rest of the bone are clearly seen.

Microscopic examination (figs. 11 and 12) revealed the central areas to consist of necrotic bony trabeculae and marrow, with the outline of fat cells still preserved in some regions. The intermediary zone showed calcification, some of it calcification of connective tissue, and some, calcification of the necrotic marrow. The outer fibrous layer was relatively acellular and shaded over at the periphery into cancellous living bone containing fatty and richly cellular hemopoietic marrow. There were numerous arteries and arterioles in the periosteum of the stump, all of which

Fig. 11 (case 3).—Photomicrograph (× 8) of the infarct at *y* in figure 10: *a* is living bone, *b* is the fibrous and calcified zone and *c* is the uninvaded portion of the infarct.

showed marked to extreme arteriosclerosis with narrowing of their lumens. In contrast, there were few arteries or arterioles to be seen in the medullary tissue, and they showed a somewhat lesser degree of arteriosclerosis. There was no sign of old thrombosed vessels within the necrotic area. The synovial lining showed slight proliferation and tag formation, with scattered infiltration with blood pigment. The articular cartilage was without notable alterations.

The central lesion was an infarct which, to judge by the advanced degree of organization, was of many years' standing. The process of replacement by new bone about the periphery seemed to have come to a standstill.

The most plausible explanation is that the lesion resulted from vascular blockage occurring in the early stages of the arteriosclerosis. However, its ancient

appearance and its stationary character as revealed in roentgenograms separated by an interval of twenty-two months is evidence that it may have developed as a result of an undetermined cause antedating the onset of the arteriosclerosis.

Arteriosclerosis of the vessels of the extremities which results in a marked degree of impairment of circulation or in gangrene has received scant consideration as a possible cause of infarction of bone. The studies of Mueller [5] and of Jaffe and Pomeranz [6] showed that a large amount of interstitial aseptic necrosis may be present in the deeper portions of the cortex even at a level considerably higher than that at which the soft

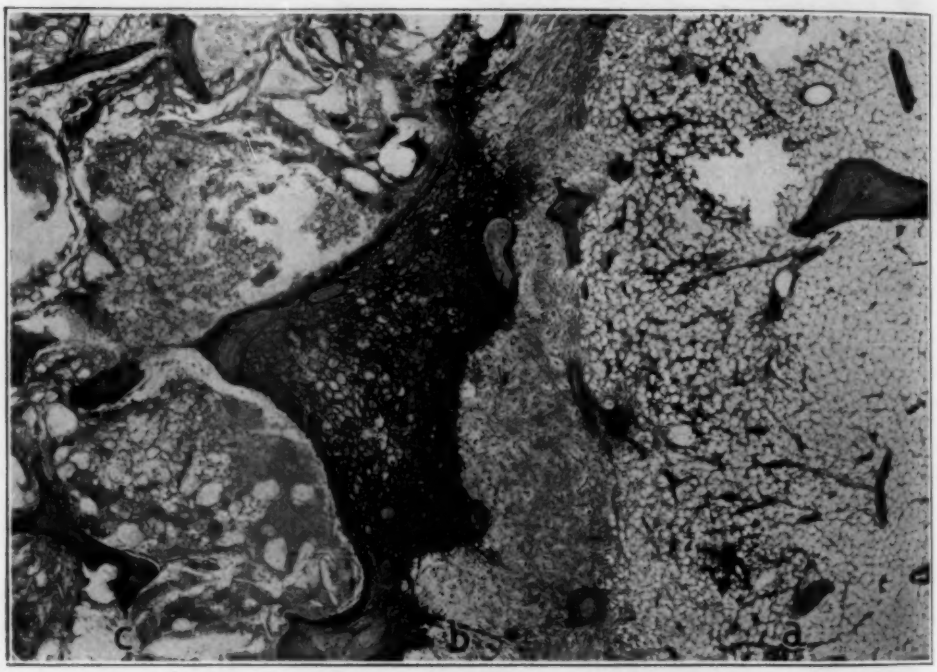

Fig. 12 (case 3).—Photomicrograph (× 21) of the right side of the wall shown in figures 10 and 11: *a* is living bone; *b* is the fibrous and calcified zone, and *c* is the uninvaded infarct.

parts become gangrenous. The latter authors reported a case of infarction of the posterior part of the body of the astragalus in a 68 year old man who had had circulatory disturbance of the foot for two years and gangrene of the toes for one year. A spreading infection finally neces-

5. Mueller, W.: Ueber das Verhalten des Knochengewebes bei herabgesetzter Zirkulation und das Bild von Nekrose der Zwischenlamellen, Beitr. z. klin. Chir. **138**:614, 1926.

6. Jaffe, H. L., and Pomeranz, M. M.: Changes in the Bones of Extremities Amputated Because of Arteriovascular Disease, Arch. Surg. **29**:566 (Oct.) 1934.

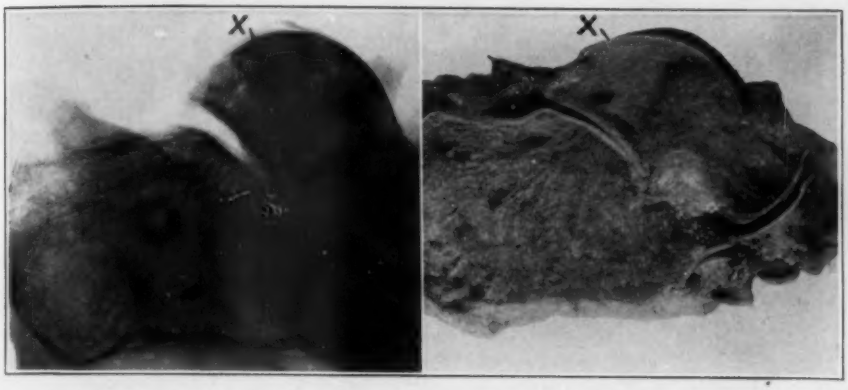

Fig. 13.—Infarct of the astragalus (*x*) in a limb amputated because of arteriosclerotic gangrene (Jaffe's case).

Fig. 14.—Microscopic section of the infarct in figure 13, surrounded by atrophic living bone.

sitated amputation through the lower part of the thigh. Sagittal section of the amputated foot showed the infarct; a photograph, a roentgenogram and a microscopic section of this infarct are reproduced here (figs. 13 and 14). Judging by the great difference in density between the infarct and the surrounding atrophic living bone, the cutting off of the circulation of the necrotic area must have occurred at least several months before the amputation. There was spreading acute infection in the vicinity, which, however, did not appear to have influenced the density of the bone. Routine roentgen examination and section of all of the bones of extremities amputated because of arteriosclerotic gangrene should be made for the purpose of establishing the frequency of such circulatory disturbances.

BONE INFARCTS AND CHRONIC HYPERTROPHIC ARTHRITIS

The cause of chronic hypertrophic arthritis is still very much in the dark. Pommer considered the primary change to be a degeneration of the articular cartilage resulting from nutritional disturbance and the subsequent changes in both cartilage and bone ends to be due to weight bearing and movement. In some cases the nutritional disturbance is assumed to arise from the trauma of ordinary use in aging or senile cartilage. In other cases changes in the underlying bone are known to precede changes in the cartilage. These are well illustrated in the cases reported here and in part I of chronic arthritis associated with extensive death of epiphysial bone in fractures of the neck of the femur, dislocation of the hip and caisson disease. This raises the question whether in other cases there are primary changes in the vessels of the subchondral bone, due to other causes, which result in nutritional interference and degeneration of cartilage with subsequent hypertrophic arthritis, since most nutrition of cartilage comes from the underlying bone. The subchondral fibroplasia in the marrow spaces, bone sclerosis and formation of cavities filled with fibrous tissue or fluid which are present in some cases are rarely associated with arteriosclerosis or with obliterative endarteritis of the vessels in the involved region. But small amounts of necrotic bone in the region of absorption and cavitation are occasionally found in microscopic examination. That hypertrophic arthritis and bone infarction may in some cases be due to a common cause is suggested by their association in the following 2 cases.

CASE 4.—An obese single woman aged 50, a graduate nurse, had slowly progressive symptoms of pain and some stiffness referable to both knees for sixteen years. She had had painful shoulders during the past four months. She had had no other major illnesses except scarlet fever at the age of 1 year and diphtheria at the age of 30.

She appeared healthy. She weieghed 190 pounds (86 Kg.). There were slight limitation and pain on motion of both knees and the left shoulder. The knees were slightly swollen and the condylar margins of the femurs were slightly

thickened. The results of physical examination were otherwise without significance. The Wassermann and Kahn reactions were negative. Roentgenograms were made of both knees. A moderate grade of osteophyte formation was present in both knees, most marked at the articular margins of the femurs and the patellas. In the right tibia (fig. 15), about 4 inches (10 cm.) below the upper end, there was the incidental finding of a centrally situated, irregularly oval shadow of increased density measuring 2 by 3 cm. There was a narrow dense rim about most of its periphery, which was more clearly demonstrated by roentgenograms of less exposure. The shadows of bone for varying distances above

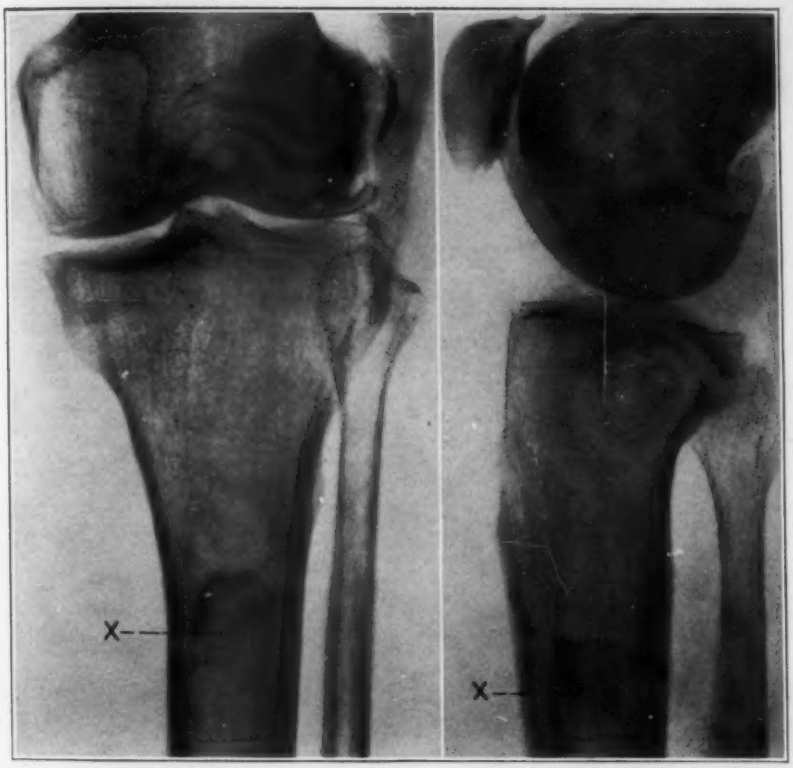

Fig. 15 (case 4).—Arthritis of the right knee had produced symptoms for ten years. An old calcified infarct of the tibia (x) had produced no symptoms.

and below were irregularly arranged, which suggested that creeping replacement of dead bone by new bone had gone on at the periphery. The diagnosis was hypertrophic arthritis of both knees and old infarct of the shaft of the right tibia, part of which was organized and the remainder calcified and stationary. On inquiry she stated that there had been no symptoms referable to the seat of the tibial lesion and no history of exposure to compressed air. Roentgen studies were then made of all of the other long bones of the extremities, but no abnormalities were noted.

Case 5.—A man aged 55 years, a locomotive engineer, for eighteen months had had frequent pains in the region of the right shoulder, sometimes radiating

down the arm and forearm, and occasionally pain in the left shoulder and arm. He had been bothered with hay fever for thirty years for which a nasal operation had been performed ten years previously. Otherwise he had suffered only minor ailments.

He appeared healthy. The musculature of the arms and shoulders was well developed. Motion was normal in the shoulders, but elevation of the arms produced pain in both shoulders and extension of the cervical part of the spine caused shoulder girdle pain. The findings were otherwise insignificant. The Wassermann and Kahn reactions were negative.

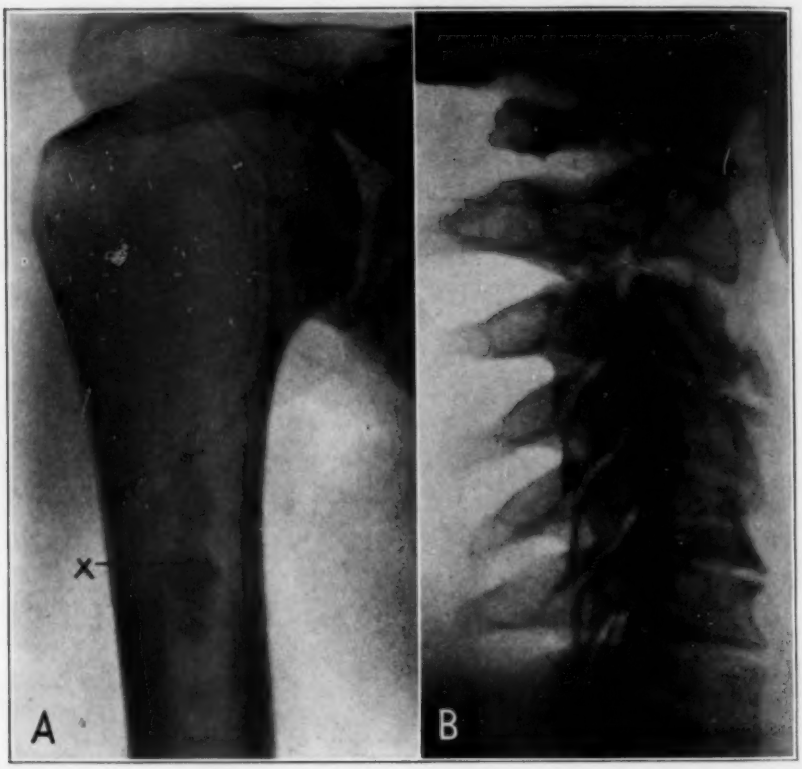

Fig. 16 (case 5).—Pains were frequent in the right shoulder and occasionally in the left for one and one-half years. The right humerus (*A*) shows a dense infarct (*x*). The cervical part of the spine (*B*) shows spondylitis with lipping.

Roentgenograms of the spine showed hypertrophic arthritis with lipping, which was marked in the cervical region and slight in the remaining portions. Roentgenograms of the right shoulder showed no changes in the joint, but an incidental finding was a beaded oblong shadow of increased density in the center of the shaft of the humerus, about 4 inches (10 cm.) below (fig. 16). Roentgenograms were then made of all of the bones and joints of the extremities. Moderate lipping was seen at the articular margins of both hip joints, but otherwise neither the bones nor the joints showed any abnormality. On inquiry the patient stated

that he had never worked in compressed air. The diagnosis was hypertrophic arthritis of the spine and hips; compression neuritis of the brachial plexuses, and old calcified infarct of the shaft of the right humerus.

In both cases the infarcts and the arthritis appeared to be of long standing, which is consistent with an etiologic relation.

Lesions similar to that in case 3 and to those of both bones and joints in the presence of caisson disease were reported by Kahlstrom, Burton and me [7] as occurring in 3 cases in which there was no history of work under compressed air, the cause remaining unknown. The remains of the infarcts in the diaphysis were old and calcified, and the deforming arthritis, when present, was in an advanced stage. Certain points in the past histories suggested various possibilities, such as fat embolism from fractures, the endarteritis of rheumatic fever and arteriosclerosis, but the case for each remained unproved. Kahlstrom has recently shown me notes on 4 more identical cases (unpublished) of multiple infarcts of bones, in 1 of which infarction followed an attack of caisson disease. A review of some of the standard illustrated textbooks on roentgen diagnosis of diseases of bone reveals roentgen pictures of infarcts that are classified under various other diagnoses.

So-called idiopathic aseptic necrosis in the head of the femur of adults with varying degrees of secondary change in the joint is relatively rare as compared with Legg-Perthes disease in children. Freund [8] first demonstrated the pathologic nature of the disease in 1926 and has subsequently [9] confirmed the findings in 3 other cases. Chandler [10] reported 2 cases proved by operation and pathologic examination in which marked obliteration of arteries of the round ligament appeared to be the cause of the necrosis. A review of the literature on chronic arthritis and that on osteochondritis dissecans of the hip reveals both roentgen and pathologic evidence that such conditions have sometimes been described under those heads. The disease occurs predominantly in men during the early and middle periods of adult life, although in Freund's first case an active stage of the disease was observed in a 77 year old woman. In most cases pain and a limp developed spontaneously and gradually, although in some their onset followed trauma. There was bilateral involvement in 4 of the 6 cases reported by Freund and

7. Kahlstrom, S. C.; Burton, C. C., and Phemister, D. B.: Aseptic Necrosis of Bone: II. Infarction of Bones of Undetermined Etiology Resulting in Encapsulated and Calcified Areas in Diaphyses and in Arthritis Deformans, Surg., Gynec. & Obst. **68**:631, 1939.

8. Freund, E.: Zur Frage des aseptischen Knochennekrose, Virchows Arch. f. path. Anat. **261**:287, 1926.

9. Freund, E.: Osteochondritis Dissecans of the Head of the Femur, Arch. Surg. **39**:323 (Sept.) 1939.

10. Chandler, F. A.: Aseptic Necrosis of the Head of the Femur, Wisconsin M. J. **35**:609, 1936.

Chandler. The symptoms in these cases ranged from one to three years in duration and simulated those of chronic hypertrophic arthritis. The roentgen and pathologic pictures resemble those of aseptic necrosis of comparable duration produced by trauma and by other conditions discussed here and will not be elaborated. The arthritic changes were those of the early stages, owing to the comparatively short duration of the disease in these cases.

The following case of bilateral involvement is of special interest in that on one side the head broke down and in six years went through the usual changes, ending with deforming arthritis, while on the other side it retained its form, the necrotic area undergoing reconstruction without the development of arthritis.

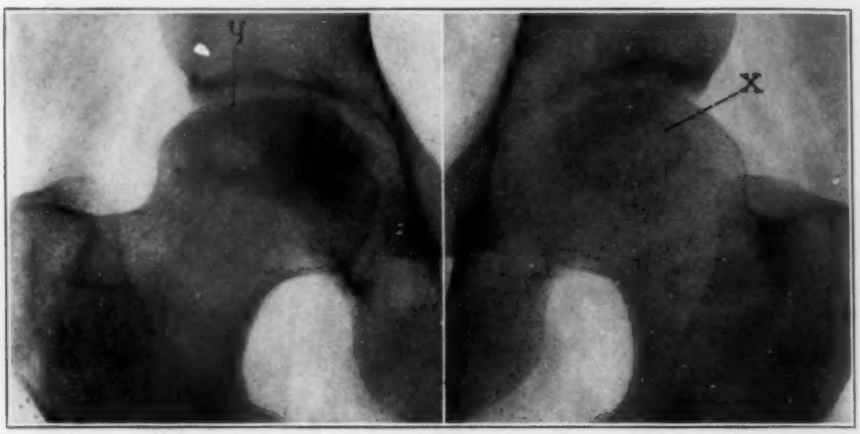

Fig. 17 (case 6).—Aseptic necrosis in the head of the femurs, with a depressed sequestrum at weight-bearing portion of the right head (*y*) and absorption of bone in the left head (*x*). Dull pain had been present in the right hip for eight months. No symptoms were present in the left hip.

Case 6.—A man aged 27 years, a laborer, complained of pain and weakness in the right hip of eight months' duration, coming on gradually without known cause and progressing slowly. At times he had also had slight pain in the left hip. He had been out of work but had continued to walk. The past history revealed only minor illnesses. The patient was short, well developed and obese. He weighed 170 pounds (77 Kg.). He walked with a slight limp in the right leg. The Wassermann and Kahn reactions were negative. The blood pressure was 124 systolic and 78 diastolic. General and regional examinations gave essentially negative results aside from the hips. The right hip showed moderate limitation of abduction and rotation. Flexion was only slightly limited but painful. The left hip was normal.

Roentgenograms revealed changes in the heads of both femurs (fig. 17). In the right head there was a break in the articular cortex opposite the superior acetabular margin, with downward displacement and flattening of the weight-

bearing portion mesial to this point. A large area of reduced density was present deep in the head, beneath the point of fracture in the cortex. There was greater density in the head in the flattened region and beneath and mesial to the area of reduced density than in the lateral portion of the head and in the neck. There were faint shadows of osteophytes at the margins of the articular cartilage of the head and at the fovea. In the head of the left femur there was an oval area of slightly reduced density in the same situation as that in the right, with a faint, narrow lateral border of increased density. It was regarded as evidence of an area of bone necrosis and absorption.

Prolonged rest in bed was considered advisable to permit reorganization of the necrotic areas and to insure the least likelihood of collapse of the head of the left femur and of further collapse and arthritis of the right. Economic conditions did not permit this program to be carried out, but the patient was able to lie or sit for the greater portion of the day and went about only for meals and for doing

Fig. 18 (case 6).—Progression of the lesions two and one-half years after figure 17 was taken. The right hip was continuously painful and stiff. The left hip had lately been slightly painful on extensive use.

chores. He was under observation for five years, and six roentgen examinations were made at intervals of nine to seventeen months. The right hip continued to be painful on use, and the limitation of motion remained about the same. The pains in the left hip gradually disappeared, and the joint was free from symptoms after two years. A roentgenogram two and one-half years later (fig. 18) showed in the right hip an extension mesially of the absorptive process, with irregular separation of the slightly more depressed and dense weight-bearing portion. There was a blurred area of increased density about the base of the head, extending laterally into the underlying neck. Lipping had increased on the head and was beginning on the margins of the acetabulum. The shadow of the articular cortex of the head below the level of the fovea was very hazy. There was a slight increase in density of the iliac cortex of the acetabulum.

In the left hip the shadow of reduced density in the head had extended mesially to the region of the fovea. It was finely trabeculated and had narrow, irregularly circinate borders of increased density. The appearance of the hip otherwise was normal.

The patient gradually became more active during the next two and one-half years, and during the last few months he performed some odd jobs. There was still a dull pain in the right hip on walking but it was less marked than before. A roentgenogram (fig. 19) taken five and one-half years after the onset of symptoms revealed in the right hip a mottled alteration in density of the depressed weight-bearing area of the head, indicating invasion by osteogenic tissue and partial replacement by living bone. The lipping of the joint margins was still more marked, as was the sclerosis of the acetabulum. In the left hip the density within the head had returned almost to normal, but the shadows of trabeculae within the old altered area were irregularly arranged and streaked in places, indicating new bone formation throughout.

In this case the indications are that on the right side the necrotic areas within the head included the entire upper portion and that absorptive changes within it so undermined and weakened the weight-bearing por-

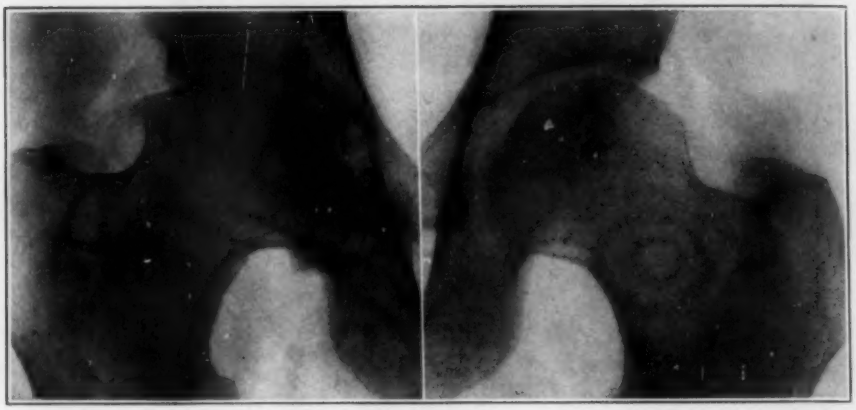

Fig. 19 (case 6).—Roentgenograms taken twenty-six months after figure 18. The left hip was symptom free and the density of the head restored almost to normal. The right hip was still painful and restricted in motion. The necrotic area (y) was mottled from creeping replacement by new bone.

tion that it caved in. Allison and Wolbach [11] and Axhausen [12] reported similar cases of absorption in the mesial condyle of the femur leading to caving in of the underlying articular cortex and the creation of an osteochondritis dissecans type of loose body. Also, I have seen metastatic carcinoma and Gaucher's disease in the head of the femur lead to the same type of collapse. The results were very slow invasion and incomplete reorganization of the necrotic area and deforming arthritis with

11. Wolbach, S. B., and Allison, N.: Osteochondritis Dissecans, Arch. Surg. **16**:1176 (June) 1928.

12. Axhausen, G.: Ueber anämische Infarkte am Knochensystem und ihre Bedeutung für die Lehre von den primären Epiphysennekrosen, Arch. f. klin. Chir. **151**:72, 1928.

permanent impairment of the joint. On the other hand, the central area of necrosis of the left head neither involved the superior portion nor so weakened it that collapse resulted. Consequently, with reorganization of the necrotic area the bone was restored practically to normal, and in the absence of extension of the process to the surface with necrosis of articular cartilage, arthritis deformans was not a sequel.

One feature of case 6, namely, the roentgen evidence of extensive absorption in the necrotic field of each head of the femur, suggests that some factor other than simple blockage of the circulation to the bone may have been active. The area of reduced density in the head of the left femur was not unlike that produced by the fibrous and cystic areas seen beneath the articular cortex of either the head or the acetabulum in cases of chronic hypertrophic arthritis, which again suggests an etiologic relation with that condition.

RELATION TO OSTEOCHONDRITIS DISSECANS

Freund regarded the lesions in his case as falling in the category of osteochondritis dissecans. However, there is some difference between this condition and that of the knee and elbow which Koenig designated as osteochondritis dissecans and which has since been repeatedly described for these and various other joints.[13] The following summary of changes is based on a personal experience with the pathologic features of more than 25 cases. In a typical case of osteochondritis dissecans, such as that of the lateral surface of the mesial condyle of the femur, which is by far the commonest site of the disease, a more or less flat oval body consisting of articular cartilage and underlying bone has its bony connections with the epiphysis severed. The cartilage often remains incompletely attached for indefinite periods, while loose fibrous connections are frequently present between the underlying surface of the body and its bed. The amount of bone in the loose body varies in different cases from a layer measuring 1 cm. or more in thickness at its central portion to nothing more than incomplete remnants of the articular cortex. The separated surfaces of both the loose body and its bony bed are found covered by a thin fibrous or fibrocartilaginous layer, and the loose fibrous attachments, when present, connect the two. Roentgenograms show the outline of the bed and also of the bony part of the loose body, whether it remains in situ or is displaced free into the joint.

Microscopic examination reveals evidence which substantiates the view that at the onset of the process there was necrosis of the bone, which, with its overlying cartilage, later became detached. In some cases the old dead bone and marrow are found practically unchanged, or there

13. Axhausen, G.: Ueber den Abgrenzungsvorgang am epiphysären Knochen (Osteochondritis dissecans), Virchows Arch. f. path. Anat. **252**:458, 1924.

may be bony detritus filling the marrow spaces, which indicates that use has broken the necrotic bone loose and that friction has produced powdered bone which has early been driven into the marrow spaces. However, if the loose body remains in its bed for some time the bone is usually invaded by blood vessels and fibrous tissue and is slowly replaced in varying degrees by new bone. The articular cartilage suffers varying degrees of nutritional disturbance, but after revascularization of the underlying bone and reestablishment of a source of nutrition by permeating serum the cartilage cells may improve in vitality and staining properties. Judging from roentgen studies, there are cases in which loose bodies become reattached and reorganized, all traces of the lesion eventually disappearing. In cases of complete detachment and of failure of revascularization the deeper portions of cartilage become necrotic and may calcify. But the superficial fibrous layer, as well as the fibrous covering of the bony surface, usually proliferates as a result of nutrition derived from the synovial fluid and forms layers of fibrocartilage, which may calcify.

There are two ways in which the usual type of osteochondritis dissecans differs from the formation of loose bodies associated with massive necrosis and consisting of articular cartilage and bone detached from the articular surface. In the first place, the surrounding bone nearly always appears normal in the roentgenograms, which indicates that all of the bone which became necrotic had been detached, whereas in the cases of massive necrosis of bone bordering on joints of the type observed in case 6 the weight-bearing portion becomes detached while the relatively large remaining necrotic portion undergoes creeping substitution by atypical new bone which is demonstrable in roentgenograms. The previously cited cases of Allison and Wolbach and of Axhausen are the only ones on record in which there was evidence of extensive involvement of surrounding bone of any sort in a case of osteochondritis dissecans bordering on the knee joint.

In the second place, the loose body in a case of osteochondritis dissecans much less frequently becomes reattached in its bed and invaded and replaced by new bone than does the loose body formed in the presence of massive necrosis of bone bordering on joints. The explanation may be the relative smallness of the body associated with osteochondritis dissecans with its greater freedom for displacement.

The theories as to the etiology of osteochondritis dissecans of the Koenig type are all more or less open to criticism. One theory is that mechanical factors in the form of weight bearing, locomotion and muscular pull bring about, through repeated compression and shearing, a gradual detachment of the most exposed portion of the end of the bone. This is strongly supported by the "microtrauma" experiments of Künt-

scher,[14] who, working with cadavers, succeeded in detaching bodies of similar size and shape from the lateral surface of the mesial condyle of the femur and from the top of the head of the femur by anchoring the bone of the proximal side of the joint and impacting the articular surfaces thousands of times by means of a revolving motor attached to the bone of the distal side of the joint. Another theory still unsubstantiated is that a single trauma either breaks the chip loose or interrupts the blood supply, after which the body gradually separates from weight bearing and absorption. Axhausen's theory [13] of bland arterial embolism meets with strong objection, especially because of the fact that there are sites of marked predilection without reason why emboli should lodge in those particular locations. Since the disease develops almost entirely during adolescence and in the first third of adult life, it is reasonably certain that arteriosclerosis is not the cause; on the other hand, this age incidence does not exclude the possibility of trauma or of some form of obliterative endarteritis. More experimental and pathologic studies will be necessary for the final solution of this question.

NECROSIS OF THE LUNATE BONE

Aseptic necrosis of the lunate bone is so well established that it will not be considered at length. The condition was first described by Kienböck as malacia following a tear of the blood vessels of its dorsal ligaments and nutritional disturbance of the bone. Preisser assumed that the tear of the blood vessels led to simple necrosis of the bone. Then followed the supposition that vascular interruption produced by a painless compression fracture results in necrosis of the bone with subsequent deformity and arthritis. Nagura [15] has recently written in support of this view, basing his claim mainly on the operative finding when the condition is "in full bloom" of a fracture line within the bone, filled with a callus of fibrocartilage. However, I have seen the same fibrocartilage filling the line of separation between the necrotic and the living portion of the head of the femur in cases of necrosis of the head complicating slipped epiphysis. Mueller [16] and Axhausen [17] each regarded the theory of a primary compression fracture as untenable in view of the absence of a history of an injury with pain at the onset and the marked

14. Küntscher, G.: Ueber das Wesen der mechanisch bedingten Knochen- und Gelenkerkrankungen, Arch. f. klin. Chir. **193**:665, 1938.

15. Nagura, S.: Die Pathologie und Pathogenese der sogenannten Lunatummalacie, Arch. f. klin. Chir. **137**:405, 1939.

16. Mueller, W.: Ueber die Erweichung und Verdichtung des Os lunatum, eine typische Erkrankung des Handgelenks, Beitr. z. klin. Chir. **119**:664, 1920.

17. Axhausen, G.: Nicht Malacie, sondern Nekrose des Os lunatum carpi, Arch. f. klin. Chir. **129**:26, 1924.

changes in form which eventually ensue. Müeller regarded the cause as undetermined, while Axhausen advanced the theory of bland embolism.

The pathologic process consists of a primary necrosis of practically all of the bone. There follows a certain amount of compression of the cancellous bone, with cloudy increased density visible in roentgenograms. The bone elongates anteroposteriorly, and vascular invasion and replacement of dead bone by new bone soon begin in the anterior and posterior regions, at the points of ligamentous insertion. Roentgenograms may then show small areas of reduced density, and, as the bone is more compressed in its longitudinal axis, fracture lines usually appear, especially running transversely beneath the proximal cortex. The line may be filled with fibrous or cartilaginous callus, and the dead crushed bone meal may be forced into the dead marrow spaces. There may be marked flattening of the bone and increase in density of much of its interior. In other cases absorption of the necrotic bone may lead to a cavitary appearance of the flattened remains. Eventually the necrotic bone is usually replaced by new bone, and the internal structure assumes more nearly the density of normal bone. Articular cartilage undergoes varying degrees of necrosis and absorption, and much of it is replaced by fibrocartilage. Hypertrophic arthritis is often eventually established in the intercarpal and radiocarpal joints. Endarteritis obliterans, such as was present in the round ligament in Chandler's cases of idiopathic necrosis of the femoral heads, has not been reported in association with this condition.

The pathologic picture in the stage of compression and partial absorption and subsitution by new bone is illustrated by the following case.

Case 7.—A man aged 20 years, while working as a steam fitter, had an aching pain and slight swelling in the right wrist. There was no history of injury, although his work necessitated much twisting of the wrist. He continued to work, but the condition slowly grew worse, so that after four months he changed to a lighter job. One month later the wrist was still unimproved. Physical examination revealed slight swelling over the front and back of the right wrist in the region of the lunate bone, and on palpation there was a slight boggy feeling in the line of the wrist joint. Motion of the wrist was moderately limited and painful in all directions. There was slight tenderness over the swelling in the region of the lunate bone. A roentgenogram (fig. 20) revealed in the anteroposterior view a slight unevenness and flattening of the proximal articular surface of the lunate bone, the density of which was slightly increased except proximally, where there was an island of reduced density bordering on the wrist joint. In the lateral view the shadow of the bone was increased in its anteroposterior diameter and shortened longitudinally, especially in its dorsal two fifths, where there was a line of reduced density suggesting a pathologic fracture. There was lipping of the anterior margin of the radius at its lower end; otherwise there were no changes in the carpal joints.

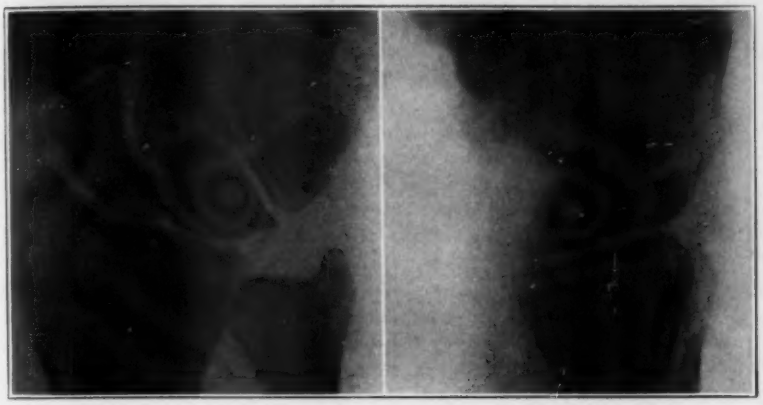

Fig. 20 (case 7).—Necrosis of the lunate bone five months after onset of symptoms.

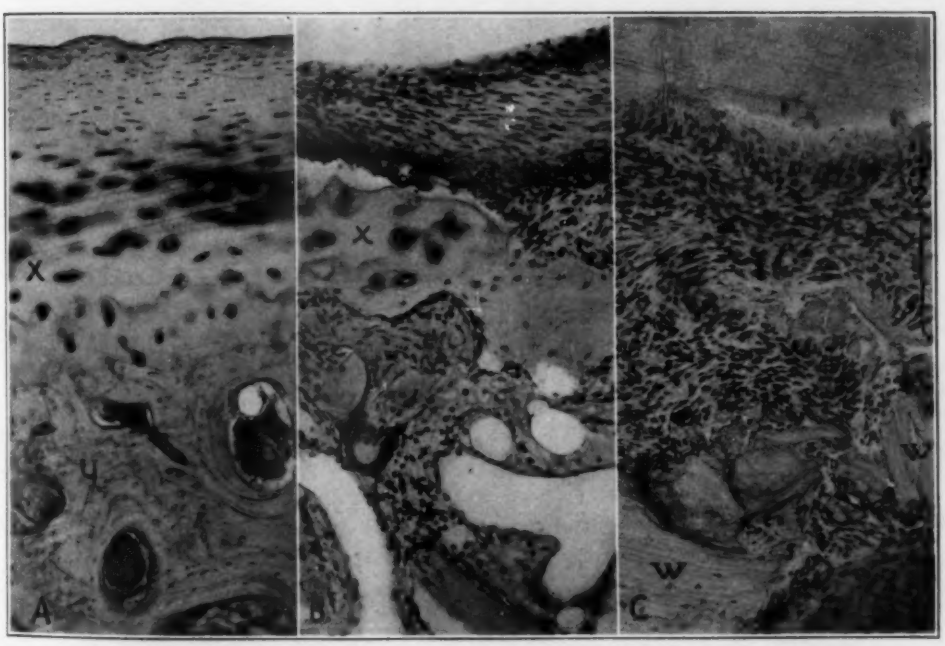

Fig. 21 (case 7).—Microscopic sections of the lunate bone, removed eight and one-half months after onset of symptoms. *A*, necrotic cortex (*y*) and poorly staining articular cartilage (*x*). *B*, zone of transformation. The cartilage (*x*) and the bone are being absorbed and replaced by new bone and fibrous marrow. *C*, dead bone (*w*) being replaced by fibrous tissue (*z*).

Aseptic necrosis of the lunate bone was diagnosed, and subsequently the diseased bone was excised. It was broken into an anterior fragment and a posterior fragment, which were flattened and elongated. Some of the articular cartilage was intact, while other regions had a fibrous overgrowth. The interior of the posterior fragment was mottled gray, with islands of bone interspersed in granulations. The anterior fragment consisted of similar material in its posterior portion, but the anterior part consisted of viable-appearing cancellous bone.

Microscopic sections confirmed the viable nature of the cancellous bone in the anterior portion, the trabeculae of which were irregular and gave the appearance of reconstruction. Sections of the middle and posterior portions showed in some regions the old articular cortex and the spongy bone for a short distance beneath to be necrotic. The overlying articular cartilage was of normal thickness, but its cartilage cells stained poorly and there was calcification in its midportion (fig. 21 *A*). In other regions the articular cortex and the cancellous bone had been absorbed and replaced by very fine living trabeculated bone and fibrous and hemopoietic marrow, while the articular cartilage was extensively necrotic, overgrown and replaced by fibrous tissue (fig. 21 *B*). The interior (fig. 21 *C*) consisted of necrotic bone, some of which had been pulverized in the compression, and fibrous tissue, which in places was absorbing the necrotic trabeculae. There were no vascular changes and very few infiltrative cells to be seen throughout the sections. The changes were those of necrosis of the entire bone with partial invasion and replacement by living bone, partial compression and erosion of trabeculae and partial replacement of necrotic bone by fibrous tissue. The articular cartilage had suffered marked nutritional impairment and in places was being replaced by fibrous tissue. That chronic hypertrophic arthritis was in the process of development was indicated by the beginning lipping of the joint margin of the lower end of the radius, visible in the roentgenogram. The cause of the necrosis remains as obscure as in the case of idiopathic necrosis of the head of the femur in adults, although traumatic factors should perhaps receive the same degree of consideration in the two conditions.

SUMMARY

Additional cases are reported of infarction and of secondary arthritis deformans due to blockage of circulation in the bone in adults indicating that the lesion is not uncommon.

Less was determined of the causation of these conditions than is usually determinable in case of infarcts of the viscera or gangrene of the limbs. Caisson disease was the established cause in 1 case, and the nature of the osseous and articular pathologic processes in caisson disease was verified in 1 of the previously reported cases by studies of the head of the femur subsequently removed at operation. Arteriosclerosis was a probable cause in another case. Illustrations are reproduced of an infarct of the talus of a limb amputated for arteriosclerotic gangrene (case of Jaffe and Pomeranz).

In 2 cases an infarct of the shaft of undetermined cause was found associated with multiple hypertrophic arthritis of distant joints, which raised the question of an etiologic relation between the two conditions.

FAMILIAL OCCURRENCE OF HYPERPLASTIC GASTRIC POLYPS

REPORT OF TWO CASES; CLASSIFICATION OF BENIGN MUCOSAL TUMORS OF THE STOMACH

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CHICAGO
AND
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The purpose of this paper is to report the occurrence of unusual benign tumor growths of the stomach in 2 members of the same family. In these cases the tumors of 2 sisters were removed surgically. The lesions were found to be histologically similar polypoid growths.

REPORT OF CASES

A 49 year old woman was seen by Dr. James I. Baltz of Detroit on Sept. 9, 1939. The history was that of epigastric distress of ten years' duration. The distress was described as a burning sensation not related to meals and occasionally relieved by administration of alkalis or change of position. There had been no loss of weight. For the past year the patient had noticed some numbness and tingling of the hands. The mother of the patient had died at the age of 64 with carcinoma of the colon. An older sister of the patient had had a gastric tumor removed in 1929 at Philadelphia. Sections of this tumor were obtained and will be described later. On physical examination there were no positive abnormalities. The stools contained no occult blood; there was no anemia, and the gastric contents contained free hydrochloric acid. Roentgen examination revealed nothing conclusive. An irregularity of the lesser curvature was noted, but no definite diagnosis was made.

Gastroscopic Examination.—This was first made by Dr. James I. Baltz on September 14, at which time he made the following observations: at depth III with the button at 7 o'clock (greater curvature at the upper portion of the fundus) there was an area apparently 4 to 5 cm. in diameter where the mucosa was thrown into moderately heavy folds; here there were redness and swelling, but no bleeding was seen; the appearance was that of mild hypertrophic gastritis.

About a month later (October 6) the patient was again studied gastroscopically by Dr. Baltz, who found the picture changed. There was less reddening of the mucosa. Several heaped-up, small, apparently polypoid areas were seen; these were roughened but not bleeding. At this time the diagnosis of polyposis of the stomach was made and was discussed with the patient.

On October 13 the patient was seen by one of us (R. S.). A very unusual lesion of the posterior gastric wall was seen gastroscopically. In depth II (mid-portion of the stomach) some folds of the greater curvature and posterior wall

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2 to 4 cm. long were seen; they were branching but completely stiff and had a beady, nodular appearance. In depth III (upper portion of the stomach) a huge foldlike protrusion (fig. 1) was observed which flattened out toward the cardia. This was entirely stiff and appeared to be infiltrated, and many surface nodes were seen. Mucosal hemorrhages, especially in the portion toward the lesser curvature, were noticed.

On November 15, examination with the gastroscope was again made. At this time the lower and upper ends of the lesion were seen, and there was definitely no sharp limit at any side. There was less bleeding at this time, but otherwise the picture was the same as that seen on the first examination. It was felt that this was a case of tumor-forming gastritis, but an infiltrating carcinoma could not be ruled out. A laparotomy with removal of a biopsy specimen from the upper posterior wall was suggested.

On November 30, a laparotomy was performed by Dr. Alexander Brunschwig. When the peritoneum was opened and the stomach examined manually, the tumor growths could not be felt, and the stomach was opened. The upper posterior wall of the stomach presented a markedly hypertrophic appearance. In this region polypoid masses could be seen. These were removed digitally, much as one would

Fig. 1.—Gastroscopic picture of a hyperplastic polyp. A huge foldlike protrusion is seen. This fold is entirely stiff and appears infiltrated; many surface nodes are visible. Two granular folds are visible in the mucosa to the left of the stomach.

pluck individual grapes from a bunch. A section of the anterior wall of the stomach was excised for histologic study.

Microscopic examination of the excised portion of the anterior wall revealed normal mucosa. This was in accord with the gastroscopic picture of the anterior wall.

The polypoid masses presented an unusual histologic appearance. The subdivisions of the growth (figs. 2 and 3) were bordered by large complex crypts, and the epithelium of the peripheral zone was variable. In the vicinity of the muscle and connective tissue core there were many cystic glands between the hyperplastic surface layer and the stalk. The majority of the glands, however, were not unlike those of the normal gastric wall except that many of them were slightly dilated. Body chief (zymogenic) and parietal (acidophilic) cells appeared in normal proportions.

The appearance of different portions of the growth was varied; nevertheless, there were no glands which appeared imperfect or frankly neoplastic. There was no evidence of any invasion of the stalk. In the growth there were areas of inter-

stitial inflammation; the predominant cells were lymphocytes and plasma cells, but eosinophils and neutrophils were numerous in some areas.

The section of the tissue taken from the sister ten years previously showed a similar type of tumor, although from a different portion of the stomach.

This section (figs. 4 and 5) represented a portion of a mucosal tumor covered by mucosa which closely resembled that of the adjacent pyloric wall. The stalk was composed of smooth muscle (connected with the muscularis mucosae), blood vessels and connective tissue, which was continuous with the submucosa. On the summit of the polypoid growth the branching prolongations of smooth muscle were thin. The gastric glands covering the stalks had the character of pyloric

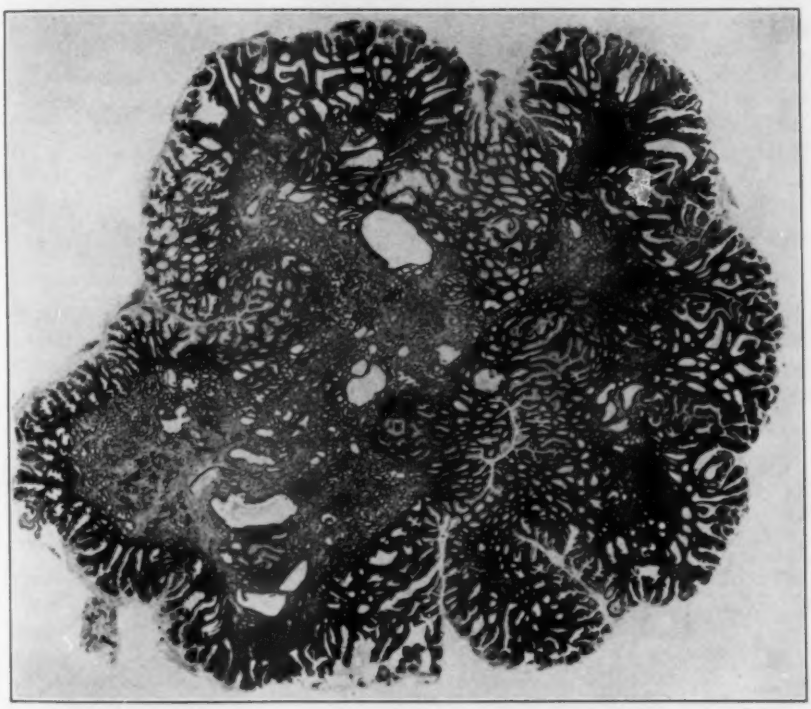

Fig. 2.—Hyperplastic polyp. The photomicrograph shows a cross section of one of the tumors seen in fig. 1. This polyp was located in the posterior gastric wall, near the cardia. Note the lack of inflammatory reaction throughout the polyp.

glands, with large mucous crypts near the surface and with small glands of the Brunner type at their base. There was very little difference between the Brunner type glands in the polyp and those in the adjacent wall. There were several dilated glands located close to the stalks. No unusual mitotic activity was noted. There were numerous interstitial cells in the papilloma and the adjacent mucosa. These consisted chiefly of plasma cells, with some eosinophils and a few neutrophils. The mucosa of the adjacent wall contained a few groups of lymphocytes in follicular formation, and there was a little perivascular infiltration of round cells in the outer layers of the muscular coat of the stomach. No inflammation of the submucosa was seen except in the stalk of the papilloma.

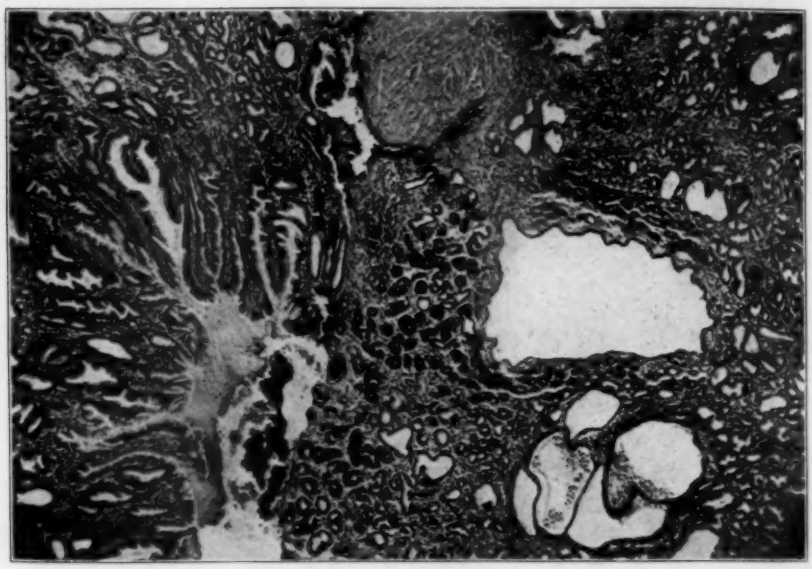

Fig. 3.—Higher magnification of a portion of the polyp seen in figure 2. Large complex crypts can be seen, and at the left a portion of the hyperplastic surface layer is visible. In the center and to the right the glands are of the type normally seen in the cardial portion of the stomach.

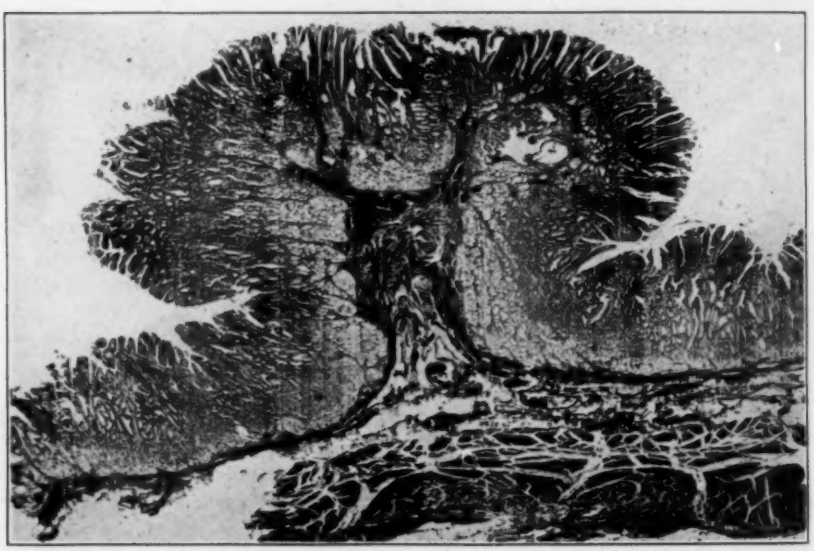

Fig. 4.—Hyperplastic polyp. The photomicrograph shows a section of the gastric tumor taken from the sister of the patient whose tumor is shown in figures 2 and 3. The polyp is composed of a smooth muscle stalk completely covered with hyperplastic mucosa. This tumor was located near the pylorus.

As seen microscopically, these growths were not true adenomatous polyps. They were hyperplastic growths of the gastric mucosa forming intragastric tumors. Such growths are very rare.

COMMENT

Classification of polypoid growths of the gastric mucosa is not easy, as these lesions are not common, and abundant histologic material is not available. This is in contrast to conditions in the intestine, where such

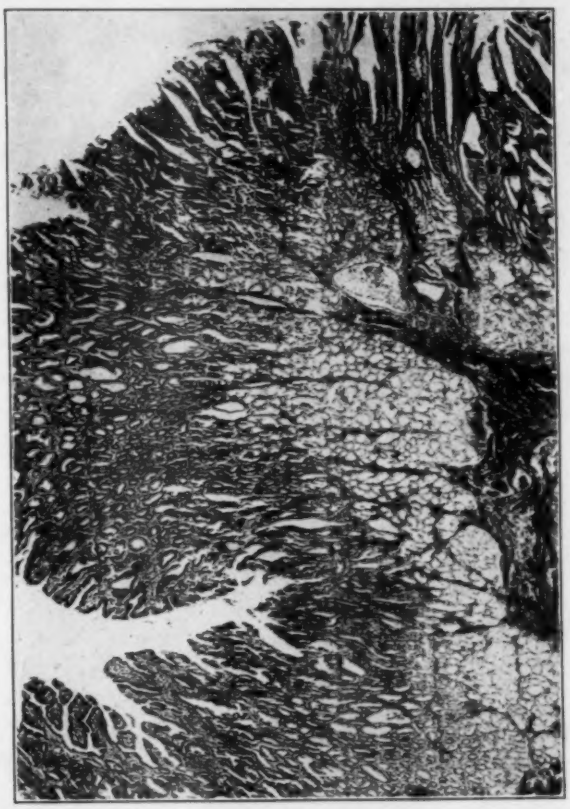

Fig. 5.—Higher magnification of the gastric wall and the edge of the polyp seen in figure 40. The gastric glands covering the stalk have the character of pyloric glands with small glands of the Brunner type at their bases. There is little difference between these glands and those of the adjacent pyloric mucosa. No evidence of inflammation is seen.

formations are frequently observed.[1] However, with the advent of roentgen relief technic and gastroscopy, it has become obvious that

1. Klemperer, P.: Studies in Adenomatous Polypi and Carcinoma of the Colon, Tr. Am. Gastro-Enterol. A., 1938, p. 88.

gastric polypoid growths are not so rare as was formerly thought. In 1936, Lawrence,[2] in 7,000 autopsies at the Cook County Hospital, observed 50 cases of gastric polyps (0.7 per cent), in 9 of which the lesions were malignant. In a series of 1,000 cases in which gastroscopic study was made by one of us (R. S.[3]), 22 cases of benign tumors were observed. Twenty (2 per cent) were benign epithelial tumors.

Even though polypoid growths of the stomach are seen much less frequently than those of the intestine, their study is easier. The many extensively ulcerative inflammations of the intestine, such as ulcerative colitis, regional ileitis and other conditions which may lead to the formation of inflammatory growths, are not seen in the stomach, although a rare form of ulcerative atrophic hyperplastic gastritis of the antrum does occur. It is possible, therefore, to make a more clearcut definition of the types of mucosal growths in the stomach.

In accordance with the present knowledge of polypoid growths of the gastric mucosa, these may be divided into three groups: (1) inflammatory pseudopolyps, which originate as compensatory formations in the presence of chronic atrophic gastritis; (2) true adenomatous polyps, and (3 hyperplastic polyps.

It cannot be stated whether transitions between these groups occur. In the discussion to follow, these groups will be considered according to (*a*) gross and microscopic appearance, (*b*) possible hereditary factors, (*c*) relation to carcinoma and (*d*) differential diagnosis.

GROSS AND MICROSCOPIC APPEARANCE OF THE THREE TYPES

1. As has been noted, severe atrophic ulcerative gastritis leading to the formation of inflammatory pseudopolyps is rare. This disease has been studied especially by Konjetzny.[4] Grossly the inflammation often is restricted to the antrum. Thick nodes of different size cover its mucosa, and between these shallow ulcerations are visible. Microscopically (fig. 6) the mucosa is thoroughly atrophic. The shallow ulcerations do not penetrate the muscularis mucosae, but severe inflammatory infiltration is seen even in the deeper layers of the gastric wall. The nodes consist chiefly of connective tissue containing numerous plasma cells, apparently representing an attempt on the part of the tissues at regeneration. They may contain atypical tubules; however,

2. Lawrence, J. C.: Gastro-Intestinal Polyps: Statistical Study of Malignancy, Am. J. Surg. **31**:499, 1936.

3. Schindler, R.: The Incidence of the Various Types of Gastric Disease as Revealed by Gastroscopic Study, Am. J. M. Sc. **197**:509, 1939.

4. Konjetzny, G. E.: Ueber de Beziehungen der chronischen Gastritis mit ihren Folgeerscheinungen und des chronischen Magensulkus zur Entwicklung des Magenkrebses, Beitr. z. klin. Chir. **85**:455, 1913.

their structure is so definitely inflammatory that they can scarcely be mistaken for true tumors.

2. True adenomatus polyps. These represent the most common type of benign gastric tumor. Adenomatous polyps are frequently solitary, but they may be multiple. Often they are seen with atrophic gastritis (especially in persons with pernicious anemia), which may be the soil for this growth. They are either broad based or pedunculated

Fig. 6.—Microscopic section of an inflammatory pseudopolyp. The glandular apparatus of the mucosa has disappeared; the mucosa is atrophic, containing many cysts of the gastric crypts and compensatory proliferation of the surface epithelium. The polypoid growth contains some atypical tubules but consists chiefly of inflammatory granulation tissue. Note the severe inflammatory invasion of the muscularis mucosae.

but always are sharply limited from the surrounding mucosa; their red color often is contrasted with the grayish pink of the surrounding atrophic mucosa. Apical ulceration may occur, but this ulceration does not prove malignancy. Histologically (fig. 7) these polyps consist

entirely of glandular tubules which present a dedifferentiated, though very regular, epithelium. Between the tubules some inflammatory cells may be observed.

3. Hyperplastic polyps. Although hyperplastic formations in the intestine seem to be frequent,[5] we have not found in the literature other cases of true hyperplastic polyp formation in the stomach. Grossly these polyps are not sharply defined; they blend with the surrounding mucosa, which appears swollen. The folds are thickened, stiff and beady or partly covered by small granules, which apparently are the first stage of the polyp formation.

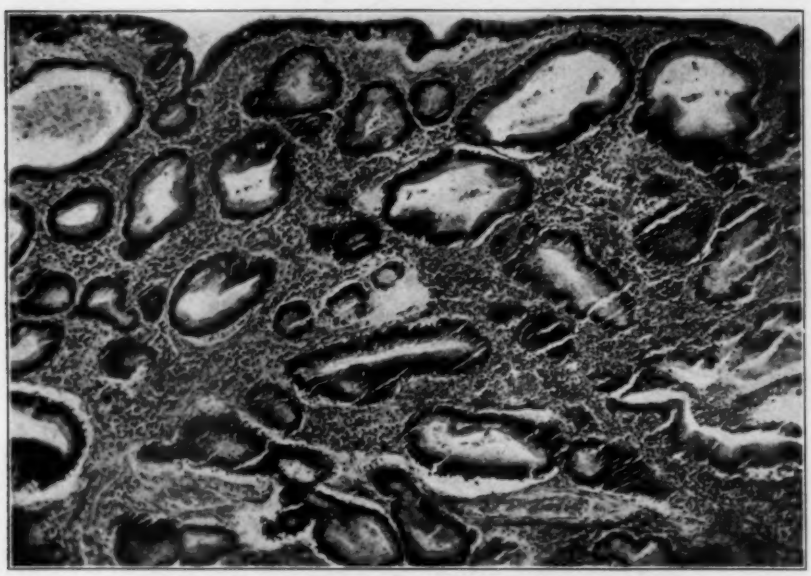

Fig. 7.—Photomicrograph of an ademalous polyp, showing the regular gland-like arrangement. There is little inflammation, and the tubules are not typical gastric glands.

Microscopically (see figs. 1, 2 and 3) the nodes consist of hyperplastic gastric mucosa, the elements of which are well differentiated. It is important to note that these growths contain the specific elements of the surrounding mucosa. This is well shown in our 2 cases; one polyp was from the upper portion of the posterior wall, showing chief cells and acidophilic cells in correct proportions. The other was a prepyloric growth and contained pyloric cells and Brunner's glands. Some inflammatory reaction was present, but it was very slight. No atrophic

5. Bargen, R. J., and Coffey, J. A.: Intestinal Polyps: Pathogenesis and Relation to Malignancy, Surg., Gynec. & Obst. **69**:136, 1939.

changes were seen, and the mucosa from a portion of the stomach remote from the lesion was normal.

HEREDITARY FACTORS

Familial occurrence of intestinal polyps is well known,[6] but some observers [7] have stated that gastric polypsois, in contrast to colonic polyposis, has no definite hereditary factors. There is no definite evidence to show any familial tendency of the first two types of gastric polypoid growths (pseudopolyps and adenomas). In this paper, however, we have presented 2 cases of a third group (hyperplastic polyps) which occurred in 2 sisters. This familial occurrence should not be considered a mere coincidence, as this condition is extremely rare. This observation seems to show that at least in the hyperplastic polypoid formations of the stomach there may be a definite heredofamilial tendency.

RELATION TO GASTRIC CARCINOMA

1. *Pseudopolyps.*—Konjetzny [8] has shown transitions from gastritis to polyp to carcinoma. There can be little doubt that atrophic gastritis with compensatory inflammatory nodes may in some cases lead to carcinoma.

2. *Adenomatous Polyps.*—Solitary or multiple adenomatous polyps arising from atrophic gastritis are generally believed to be precancerous lesions. When multiple benign adenomas are found, one of which shows carcinomatous degeneration, a definite relation can scarcely be doubted.[9] Miller and his associates [10] reported cases of adenomatous polyp in which carcinomatous degeneration was observed. It seems, however, that the gradual development of a certainly benign tumor into carcinoma has not yet been observed clinically. In 1 case of our own observation [11] a small filling defect was observed at roentgen examination three years before surgical removal of a polypoid carcinoma grow-

6. Tønnesen, H.: Polyposis Gastrointestinalis, Acta chir. Scandinav. **68** (supp 17):1, 1931. Wechselmann, L.: Polyp und Carcinom im Magen-Darmkanal, Beitr. z. klin. Chir. **70**:855, 1910. Lockhart-Mummery, P.: Cancer and Heredity, Lancet **1**:427, 1925.

7. Brunn, H., and Pearl, F.: Multiple Gastric Polyposis, Am. J. Surg. **40**:51, 1938.

8. Konjetzny, G. E.: Beziehungen der chronischen Gastritis zum Magenkrebs, Verhandl. d. deutsch. Gesellsch. f. Chir. **43** (pt. 1):65, 1914.

9. Menétrier, P.: Des polyadénomes gastriques et de leurs rapports avec le cancer de l'estomac, Arch. de physiol. norm. et path. **1**:236, 1888.

10. Miller, T. G.; Eliason, E. L., and Wright, V. W. M.: Carcinomatous Degeneration of Polyp of the Stomach, Arch. Int. Med. **46**:841 (Nov.) 1930.

11. Schindler, R., and Gold, R. L.: Gastroscopy in Early Carcinoma, Surg., Gynec. & Obst. **69**:1 (July) 1939.

ing in an atrophic mucosa. It is not certain that three years is a long enough period to prove the benign nature of the growth at the time of its origin.

3. *Hyperplastic Polyps.*—Nothing is known about the relation of the hyperplastic polyp to carcinoma. One of our patients, operated on ten years ago, is living and well at present; and the other patient, operated on in November 1939, is living and gaining weight. It is notable, however, that the mother died of carcinoma of the colon, although this could be purely coincidental. It should be remembered, however, that hyperplastic changes in the intestine have a definite relation to carcinoma.[5]

DIFFERENTIAL DIAGNOSIS

1. The correct diagnosis of the inflammatory formation of pseudopolyps is difficult. However, the roentgen picture of round, regular filling defects together with narrowing of the antrum may suggest this form. At gastroscopic examination the differential diagnosis between pseudopolyps and infiltrating carcinoma with superficial ulcerations seems to be impossible.

2. The true adenomas are easily diagnosed gastroscopically. The picture is characteristic, consisting of red elevations covered by mucosa on the background of the thinned, grayish, atrophic mucosa. The elevations are pedunculated or broad based and rarely ulcerated. The picture is typical and not likely to be mistaken. The diagnosis of early carcinomatous change may be difficult, however; this remains to be seen. At roentgen examination small, round, sharply defined filling defects are sometimes seen. For the diagnosis of small adenomas gastroscopic study is the superior method.

3. The differential diagnosis of the third type, the hyperplastic polyp, has proved unexpectedly difficult. The first observer in our case (Dr. Baltz) diagnosed hypertrophic gastritis of the posterior wall on his first examination but later saw and described with eminent correctness the origin of benign tumors in this area. When one of us (R. S.) examined the patient the tumors could no longer be discerned. They had grown so closely together and so close was the connection between them and the surrounding hyperplastic mucosa that tumor simulating gastritis and carcinoma were the only diagnoses considered.

SUMMARY

In 2 sisters, hyperplastic polyps originating from a hyperplastic mucosa were found. The lesions were located in 1 case in the upper portion of the posterior wall of the stomach and in the other in the pyloric antrum. The microscopic picture of these formations is described.

Comparison of these lesions with other polypoid growths of the stomach leads to a division of gastric polypoid growths into three groups: (1) inflammatory pseudopolyps; (2) adenomatous polyps, and (3) hyperplastic polyps.

The gross and microscopic pictures of the three groups are described. The possible role of hereditary factors, the relation to carcinoma and the differential diagnosis are discussed.

The first patient was referred to us by Dr. James I. Baltz, who also reported the clinical data. The material in the case of the second patient was supplied by Dr. John H. Gibbon Jr. and Dr. John Bauer, pathologist at the Pennsylvania Hospital in Philadelphia. The study and description of the microscopic sections are the contribution of Dr. Eleanor M. Humphreys.

COMPARATIVE CONCENTRATION OF HUMAN HEPATIC BILIRUBIN AND CHOLESTEROL BY THE GALLBLADDER

A POSTMORTEM STUDY

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Many studies on bile and its constituents have been made in the past. Most of these have been directed simply to determining the absolute amounts of the various constituents. In man, these studies have been of three types: (1) on gallbladder bile taken at operation; (2) on bile taken postoperatively from a hepatic fistula, and (3) on gallbladder bile taken post mortem. Comparisons have been made between the first and second and between the second and third types of determination. That any of the determinations are truly physiologic may be debated—the very fact that operation on the biliary tree was required impugns the validity of the results. McNee [1] pointed out that most results and methods are unsatisfactory. The present study differs from the former ones in that the hepatic bile used for these determinations was taken at the same time as the gallbladder bile in cases in which operation on the biliary tree had not been performed and in which the gallbladder and the liver were grossly normal.

There is a second group of determinations in the literature, on experimental animals. These were taken more or less simultaneously, and comparisons were made. However, man is the only animal in which cholesterol stones are common, particularly in the aged.[2]

The objective in this paper is to compare the concentration of hepatic cholesterol by the gallbladder with the concentration of hepatic bilirubin by that organ. The analyses were all done on specimens obtained post mortem. It is hoped that by these comparisons it will be possible to determine whether the gallbladder decreases by absorption, increases

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Work done in the Section on Pathologic Anatomy, and the Division of Biochemistry, the Mayo Clinic.

1. McNee, J. W.: Cholesterin: An Account of Its Relations to Pathology and Physiology, Quart. J. Med. **7**:221-236 (April) 1914.

2. Mentzer, S. H.: A Clinical and Pathologic Study of Cholecystitis and Cholelithiasis, Surg., Gynec. & Obst. **42**:782-793 (June) 1926.

by secretion or simply concentrates the hepatic cholesterol which is delivered to it. Besides this, certain factual data will be presented for the first time. Only two references can be found relative to determinations on postmortem hepatic bile.[3] Newer and more delicate quantitative analyses now make these determinations feasible, though they are still difficult and frequently subject to error that is too great.

REVIEW OF THE LITERATURE

Various investigators have made determinations of the quantities of cholesterol and bilirubin in hepatic and in gallbladder bile. Many of these figures antedate satisfactory experimental or clinical methods, but even recent workers have obtained widely varying results. The values for hepatic bilirubin obtained by various investigators vary from 1.15 to 128 mg. per hundred cubic centimeters.[4] Those for hepatic cholesterol vary from 0 to 2.32 Gm. per hundred cubic centimeters.[5]

A similar situation is evident on study of the determinations found in the literature for gallbladder bilirubin and cholesterol. The quantities of bilirubin vary from 3.5 mg. per hundred cubic centimeters for healthy normal subjects to as high as 1,786 mg. per hundred cubic centimeters.[6]

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3. (*a*) Elman, R., and Taussig, J. B.: The Cholesterol Function of the Gall Bladder, J. Exper. Med. **54**:775-787 (Nov.) 1931. (*b*) Fox, F. W.: The Composition of Human Bile and Its Bearing upon Sterol Metabolism, Quart. J. Med. **21**:107-121 (Oct.) 1927.

4. (*a*) Antic, D., and Goropevsek, M.: Cholesterin und Bilirubin in der Galle und ihr diagnostischer Wert, Arch. f. Verdauungskr. **61**:334-343, 1937. (*b*) Elton, N. W.: Bilirubin Concentrations in the Human Gallbladder, Am. J. Clin. Path. **6**:81-90 (Jan.) 1936. (*c*) Greene, C. H.; Walters, W., and Frederickson, C. H.: The Composition of the Bile Following the Relief of Biliary Obstruction, J. Clin. Investigation **9**:295-310 (Dec.) 1930. (*d*) Newman, C.: Physiology of the Gall-Bladder and Its Functional Abnormalities: I. Physiology, Lancet **1**:785-791 (April 15) 1933; II. Disorders of Motility, ibid. **1**:841-848 (April 22) 1933; III. Abnormalities of Concentration and Secretion in the Gall-Bladder, ibid. **1**:896-901 (April 29) 1933. (*e*) Rosenbloom, J.: A Quantitative Chemical Analysis of Human Bile, J. Biol. Chem. **14**:241-244, 1913. (*f*) Schöndube, W., and Kalk, H.: Ueber moderne Methoden in der Diagnostik der Gallenblasenerkrankungen, Med. Klin. **21**:1949-1952 (Dec. 24) 1925. (*g*) Elman and Taussig.[3a]

5. (*a*) Bockus, H. L., and Eiman, J.: Experimental and Clinical Significance of the Cholesterol Content of the Bile, Arch. Int. Med. **34**:161-167 (Aug.) 1924. (*b*) Bronner, H.: Wasserstoffionenkonzentration der Galle und Steinbildung, Arch. f. klin. Chir. **180**:597-599, 1934. (*c*) Riegel, C.; Ravdin, I. S.; Morrison, P. J., and Potter, M. J.: Studies of Gallbladder Function: XI. The Composition of the Gallbladder Bile in Pregnancy, J. A. M. A. **105**:1343-1344 (Oct. 26) 1935. (*d*) Elman and Taussig.[3a] Fox.[3b] Antic and Goropevsek.[4a] Rosenbloom.[4e]

6. Mentzer.[2] Elman and Taussig.[3a] Antic and Goropevsek.[4a] Elton.[4b] Schöndube and Kalk.[4f]

The quantities of cholesterol vary from less than 50 mg. to 17.6 Gm. per hundred cubic centimeters.[7] Various explanations are current as to the reasons for these variations and their significance in the theoretic considerations to which these data are applied.[8]

There are four distinct opinions as to the activity of the gallbladder in regard to biliary cholesterol: (1) that the gallbladder absorbs cholesterol from the bile;[9] (2) that it secretes cholesterol into the bile;[10] (3) that it simply concentrates biliary cholesterol *pari passu* with the

7. (*a*) Andrews, E.: Detailed Studies of a Series of Gall-Bladder Cases, Surg., Gynec. & Obst. **57**:36-50 (July) 1933. (*b*) Andrews, E.; Hrdina, L., and Dostal, L. E.: Etiology of Gallstones: II. Analysis of Duct Bile from Diseased Livers, Arch. Surg. **25**:1081-1089 (Dec.) 1932. (*c*) Fowweather, F. S., and Collinson, G. A.: Certain Chemical Changes Associated with Gall-Stones, with Special Reference to the Relation Between Gall-Stones and Hypercholesterolaemia, Brit. J. Surg. **14**:583-608 (April) 1927. (*d*) Newman, C. E.: Beitrag zum Studium der Gallenniederschlags- und Gallensteinbildung, Beitr. z. path. Anat. u. z. allg. Path. **86**:187-200, 1931. (*e*) Ravdin, I. S.; Riegel, C.; Johnston, C. G., and Morrison, P. J.: Studies in Biliary Tract Disease, J. A. M. A. **103**:1504-1509 (Nov. 17) 1934. (*f*) Riegel, C.; Ravdin, I. S.; Johnston, C. G., and Morrison, P. J.: Studies of Gall-Bladder Function: XIII. The Composition of the Gall-Bladder Bile and Calculi in Gall-Bladder Disease, Surg., Gynec. & Obst. **62**:933-940 (May) 1936. (*g*) Elman and Taussig.[3a] Fox.[3b] Antic and Goropevsek.[4a] Newman.[4d] Rosenbloom.[4e] Bockus and Eiman.[5a] Riegel and others.[5e]

8. Andrews, E.; Schoenheimer, R., and Hrdina, L.: Etiology of Gallstones: I. Chemical Factors and the Rôle of the Gallbladder, Arch. Surg. **25**:796-810 (Oct.) 1932. Fitz, R., and Aldrich, M.: Clinical Observations on Certain Constituents of the Bile, J. A. M. A. **79**:2129-2132 (Dec. 23) 1922. Ivy, A. C.: Physiology of the Gallbladder, Physiol. Rev. **14**:1-102 (Jan.) 1934. Riegel, C.; Ravdin, I. S., and Rose, H. J.: Studies of Gallbladder Function: XV. Cholesterol in Human Liver Bile, J. Clin. Investigation **16**:67-72 (Jan.) 1937. Whipple, G. H.: The Origin and Significance of the Constituents of the Bile, Physiol. Rev. **2**: 440-459 (July) 1922. Elton.[4b] Greene and others.[4c] Newman.[4d] Bockus and Eiman.[5a] Bronner.[5b] Andrews and others.[7b] Ravdin and others.[7e]

9. (*a*) Aschoff, L.: Wie entstehen die reinen Cholesterinsteine? München. med. Wchnschr. **60**:1753-1756 (Aug. 12) 1913; (*b*) Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924, pp. 181 and 206. (*c*) Boyd, W.: Gall-Bladder Problems, Canad. M. A. J. **12**:689-693 (Oct.) 1922. (*d*) Mentzer, S. H.: Cholesterosis of the Gallbladder, Am. J. Path. **1**:383-388 (July) 1925. (*e*) Winkenwerder, W. L.: A Study of Resorption from the Biliary Tract with Especial Reference to the Morphology and Permeability of the Cystic Epithelium, Bull. Johns Hopkins Hosp. **46**:272-295, 1930; (*f*) A Study of the Lymphatics of the Gall-Bladder of the Cat, ibid. **41**:226-238, 1927. Antic and Goropevsek.[4a]

10. Elman, R., and Graham, E. A.: The Pathogenesis of the "Strawberry" Gallbladder, Arch. Surg. **24**:14-22 (Jan.) 1932. Naunyn, B.: Die Gallensteine, ihre Entstehung und ihr Bau, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **33**:1-54, 1921. Elman and Taussig.[3a] Ravdin and others.[7e]

other biliary constituents,[11] and (4) that its activity varies with the relative concentration of cholesterol in the blood and bile.[12]

METHODS

The bile was obtained as soon as possible at postmortem examination. Many cases proved unsuitable for study, since any number of conditions supervened, such as previous cholecystectomy, cholelithiasis with or without cholecystitis, hepatic atrophy, hepatic cirrhosis, jaundice of any type, limited examinations and so forth. In the satisfactory cases the intestines were removed first, and then the extrahepatic biliary tree was exposed. With as little disturbance to the gallbladder as possible, a hemostat was placed on the cystic duct and a second on the common hepatic duct. Then the liver and gallbladder were removed together.

The hepatic bile was aspirated from the hepatic ducts by a small syringe and a blunt needle of large caliber. Occasionally, apparently empty ducts can be made to yield a sufficient quantitity by pressure on the substance of the liver. Care must be exercised to avoid contamination by gallbladder bile or blood. The bile of the normal-appearing gallbladder was then aspirated with a sharp needle of similar bore. The specimens were kept in the ice box until examined.

The chemical determinations were carried out in the following manner: As little as 0.2 cc. of hepatic bile may prove sufficient for the determinations. The larger the quantity of bile obtained, the more accurate are the determinations. The bile is first diluted with distilled water in order to make a satisfactory bilirubin determination. One cubic centimeter of gallbladder bile is used and all the hepatic bile obtained. Dilution is carried out until the diluted bile is somewhat darker than a mildly icteric blood serum. All cellular debris or sediment in the 15 cc. graduated test tubes used for collecting and measuring the bile is shaken until it is homogeneously suspended throughout. For bilirubin determinations the hepatic dilution may vary from five to thirty times and the cholecystic dilution from ten to one hundred and fifty times. One cubic centimeter of the diluted specimen is used for the bilirubin determination (according to the technic of Gibson and Goodrich[13]), which is recorded as milligrams per hundred cubic centimeters. In each instance the rest of the diluted hepatic bile is run for the cholesterol content according to the technic of Elman and Taussig.[14] For the determinations of gallbladder

11. Andrews, E.; Dostal, L. E.; Goff, M., and Hrdina, L.: Mechanism of Cholesterol Gall-Stone Formation, Ann. Surg. **96**:615-623 (Oct.) 1932. Andrews, E.; Dostal, L. E., and Hrdina, L.: Etiology of Gallstones: IV. Is Cholesterol Excreted by the Gallbladder Mucosa? Arch. Surg. **26**:382-388 (March) 1933. Riegel, C.; Johnston, C. G., and Ravdin, I. S.: Studies on Gall Bladder Function: VIII. The Fate of Bile Pigment and Cholesterol in Hepatic Bile Subjected to Gall Bladder Activity, J. Exper. Med. **56**:1-13 (July) 1932. Riegel, C.; Ravdin, I. S., and Johnston, C. G.: Studies of Gall-Bladder Function: VI. The Absorption of Bile Salts and Cholesterol from the Bile-Free Gall Bladder, Am. J. Physiol. **99**:656-665 (Feb.) 1932. Fox.[8b] Riegel and others.[7f] Winkenwerder.[9f]

12. Wilkie, A. L., and Doubilet, H.: Passage of Cholesterol Through the Mucosa of the Gallbladder, Arch. Surg. **26**:110-121 (Jan.) 1933.

13. Hawk, P. B.: Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son & Co., 1937.

14. Elman, R., and Taussig, J. B.: The Quantitative Determination of Cholesterol in the Bile, J. Lab. & Clin. Med. **17**:274-279 (Dec.) 1931.

cholesterol, 1 cc. of ten times diluted bile is used. The results are reported as milligrams per cubic centimeter.

The bilirubin determinations are done according to the technic of Gibson and Goodrich. To 1 cc.[15] of diluted bile in a 15 cc. graduated tube is added 1 cc. of Ehrlich's diazo reagent, and the mixture is shaken. When the color is fully developed, 2 cc. of saturated ammonium sulfate solution is added. Then 9 cc. of 95 per cent alcohol brings the solution to 13 cc., and the solution is shaken vigorously. The solution is made to the 15 cc. mark with concentrated hydrochloric acid and stirred thoroughly. After five to ten minutes it is filtered and read against a pure bilirubin standard, previously prepared.

The unknowns to be used for the cholesterol determinations are mixed with 6 cc. of 95 per cent alcohol. This is heated in a water bath to 70 C. for a few minutes and filtered, which removes most of the bilirubin and protein. The resulting alcoholic solution is extracted three times with purified petroleum benzine U. S. P. (petroleum ether) in a separatory funnel; one uses in all about 100 cc. of purified petroleum benzine. This is evaporated to dryness on a water bath. The residue is taken up in chloroform, and the determination is made against a simultaneously determined standard solution.

RESULTS

The results obtained in the present investigation are summarized in the accompanying tables. Thirty-one cases were studied. These could be subdivided into three fairly definite groups: (1) cases in which the concentration of bilirubin and cholesterol was approximately equal —19 of the 31 cases (table 1); (2) cases in which the relative concentration of the bilirubin was greater than that of cholesterol, indicating absorption of cholesterol—8 cases (table 2), and (3) cases in which the relative concentration of the cholesterol was greater than that of bilirubin —4 cases (table 3).

With the exception of the report of Elman and Taussig [3a] no other paper presents such data as these simultaneous determinations of hepatic and gallbladder cholesterol and bilirubin.

Wide variations in the bilirubin and cholesterol content in both hepatic and gallbladder bile existed in all three groups. In group 1 (table 1) the extreme variations for the hepatic bilirubin were 96 to 1,720 mg. per hundred cubic centimeters and for the gallbladder bilirubin were 96 to 6,000 mg. per hundred cubic centimeters. The ratios of concentration of the hepatic bilirubin varied from 0.96 to 24.5. The value for hepatic cholesterol was as low as 0.25 mg. and as high as 7.81 mg. per cubic centimeter. The cholesterol content per cubic centimeter of bile from the gallbladder was from 0.8 mg. to 17.85 mg. The ratio of cholesterol in the gallbladder bile to cholesterol in the liver bile varied from 0.6 to 21.4.

15. Gibson and Goodrich [13] used 2 cc. of serum. Therefore, these results are multiplied by 2 to get results in milligrams per hundred cubic centimeters.

TABLE 1.—*Comparative Concentration of Hepatic Bilirubin and Cholesterol by the Gallbladder in White Subjects: Cases in Which the Concentration of Bilirubin and That of Cholesterol Was Approximately Equal*

Embalmed	Age, Years	Sex	Hepatic Bilirubin, Mg. per 100 Cc.	Gallbladder Bilirubin, Mg. per 100 Cc.	Ratio of Gallbladder Bilirubin to Hepatic Bilirubin	Hepatic Cholesterol, Mg. per Cc.	Gallbladder Cholesterol, Mg. per Cc.	Ratio of Gallbladder Cholesterol to Hepatic Cholesterol	Cause of Death	Gross Pathologic Change (Liver, Gallbladder, Bile Ducts)
—	42	F	912	1,560	1.7	1.5	3.33	2.2	Malignant glioma; bronchopneumonia	.....
+	29	M	230	3,540	15.4	0.5	7.5	15.0	Malignant glioma; bronchopneumonia	Gallbladder: cholesterol polyps
+	50	M	200	4,905	24.5	0.25	5.36	21.4	Carcinoma of lung; cerebral metastasis	.....
+	63	M	1,720	2,520	1.5	7.81	9.09	1.2	Nephrolithiasis; pyelonephritis; icterus grade 2*; bronchopneumonia	Gallbladder: cholesterosis grade 2*
+	67	M	528	1,995	3.8	3.31	12.0	3.6	Chronic duodenal ulcer; bronchopneumonia	Liver: atrophy grade 1+*
—	52	F	540	1,540	2.9	2.47	12.0	4.9	Calcareous aortic stenosis; dilatation of left ventricle	Cysts of liver
—	48	F	512	1,570	3.1	3.6	13.34	3.7	Exophthalmic goiter; hemorrhage	Gallbladder: cholesterosis grade 2*
+	30	F	160	186	1.2	3.64	6.0	1.6	Aneurysm of circle of Willis; rupture with hemorrhage	.....
+	38	M	112	547.5	4.9	2.22	9.0	4.1	Carcinoma of larynx; bronchopneumonia	Gallbladder: cholelithiasis, cholesterol polyps
+	41	M	504	2,628	5.2	6.57	17.85	2.7	Adenomatous goiter; bronchopneumonia	Liver: subcapsular lipoma
—	33	F	1,038	6,000	5.8	1.16	10.0	8.6	Nephrectomy for tuberculosis; pulmonary edema with beginning pneumonia	Cystic duct joined right hepatic duct
+	65	M	96	286	3.0	0.74	3.34	4.5	Appendectomy for gangrene; peritonitis; pulmonary embolism	Gallbladder: numerous cholesterol polyps
—	77	M	246	410	1.7	3.0	7.5	2.5	Aneurysm abdominal aorta; hemorrhage	Liver: few scattered hyaline tubercles
—	93	F	115.2	159	1.4	0.45	0.8	1.8	Erysipelas of face	Gallbladder: 6 black stones
—	54	M	510	5,700	11.2	0.625	8.33	13.3	Carcinoma of sigmoid flexure; pelvic peritonitis; bronchopneumonia	Gallbladder: cholesterol polyps, cholesterosis grade 2*
—	71	M	670	1,320	2.0	1.25	2.14	1.7	Gastrojejunal ulcer; bronchopneumonia	Gallbladder: cholesterosis grade 1*
—	63	M	840	2,368	2.8	1.876	5.555	3.0	Cerebral arteriosclerosis grade 4*; bilateral bronchopneumonia	.....
—	81	M	100	96	0.96	1.575	1.0	0.6	Bronchopneumonia	Gallbladder; cholesterol stone, mucosal scarring, cholesterosis grade 1*
—	64	M	1,215	4,200	3.5	1.023	4.2	4.1	Carcinoma of colon; intestinal obstruction	Gallbladder: cholesterol polyp; liver: multiple metastases

* On a basis of 1 to 4.

A similar variation in all aspects was found in the cases in group 2, which are classified together on the basis of a higher bilirubin concentration than cholesterol concentration (table 2). In these 8 cases the concentration of bilirubin in the hepatic bile varied from 112 to 1,572

TABLE 2.—*Comparative Concentration of Hepatic Bilirubin and Cholesterol by the Gallbladder in White Subjects: Cases in Which the Concentration of Bilirubin Was Greater Than That of Cholesterol*

Embalmed	Age, Years	Sex	Hepatic Bilirubin, Mg. per 100 Cc.	Gallbladder Bilirubin, Mg. per 100 Cc.	Ratio of Gallbladder Bilirubin to Hepatic Bilirubin	Hepatic Cholesterol, Mg. per Cc.	Gallbladder Cholesterol, Mg. per Cc.	Ratio of Gallbladder Cholesterol to Hepatic Cholesterol	Cause of Death	Gross Pathologic Change (Liver, Gallbladder, Bile Ducts)
+	55	F	248	2,920	11.8	2.14	13.64	6.4	Rheumatic heart disease; dilatation of left ventricle	Liver: congestion with atrophy, grade 2*
+	50	M	112	1,980	17.7	2.22	10.0	4.5	Carcinoma of stomach; bronchopneumonia	.....
—	60	M	1,572	3,836	2.4	13.3	12.36	0.9	Aneurysm of aorta; rupture with hemorrhage	.....
+	32	M	292	1,424	4.9	3.33	6.25	1.9	Lindau's disease; internal hydrocephalus, grade 2+*	Liver: small cyst left lobe; gallbladder: many small cholesterol polyps, cholesterosis, grade 1*
+	32	M	350	2,880	8.2	1.85	6.8	3.7	Acute purulent cerebrospinal meningitis	Gallbladder: cholesterol polyps, numerous small stones
+	18	F	320	1,260	3.9	5.35	6.82	1.3	Abscess left temporoparietal region	.....
—	31	M	200	1,650	8.25	1.17	2.68	2.3	Tuberculosis (pulmonary and osseous); bronchopneumonia	.....
—	66	M	240	1,498	6.2	4.28	9.375	2.2	Spongioblastoma; hemorrhagic edema of lungs	.....

* On a basis of 1 to 4.

mg. per hundred cubic centimeters and in the gallbladder bile from 1,260 to 3,836 mg. per hundred cubic centimeters. The ratio of bilirubin concentration by the gallbladder varied from 2.4 to 17.7. The concentration of cholesterol varied from 1.17 to 13.3 mg. per cubic centimeter in the hepatic bile and from 2.68 to 13.64 mg. per cubic centimeter in the bile from the gallbladder. The ratio of cholesterol concentration was from 0.9 to 6.4.

Group 3 (table 3), in which the cholesterol concentration was higher than the bilirubin concentration, showed unusually high values for hepatic bilirubin. In these 4 cases, this value varied from 240 to 1,200 mg. per hundred cubic centimeters. The value for bilirubin in the gallbladder was likewise high. The lowest figure was 1,080 mg., and the highest, 2,040 mg., per hundred cubic centimeters. The ratio between the amount of gallbladder bilirubin and hepatic bilirubin varied between 1.6 and 6.2. The cholesterol values were from 0.416 to 4.26 mg. per cubic centimeter for the hepatic bile and from 4.5 to 17.18 mg. per cubic

TABLE 3.—*Comparative Concentration of Hepatic Bilirubin and Cholesterol by the Gallbladder in White Subjects: Cases in Which the Concentration of Cholesterol Was Greater Than That of Bilirubin*

Embalmed	Age, Years	Sex	Hepatic Bilirubin, Mg. per 100 Cc.	Gallbladder Bilirubin, Mg. per 100 Cc.	Ratio of Gallbladder Bilirubin to Hepatic Bilirubin	Hepatic Cholesterol, Mg. per Cc.	Gallbladder Cholesterol, Mg. per Cc.	Ratio of Gallbladder Cholesterol to Hepatic Cholesterol	Cause of Death	Gross Pathologic Change (Liver, Gallbladder, Bile Ducts)
+	53	F	393.3	1,080	2.7	1.5	10.0	6.7	Carcinoma of colon; pulmonary embolism	.....
+	57	M	392.0	2,040	5.2	0.416	15.0	36.1	Carcinoma of rectum; generalized peritonitis	Liver: echinococcus cyst (?)
—	42	F	1,200.0	1,900	1.6	4.26	17.18	4.0	Abscess of brain; increased intracranial pressure	.....
—	60	F	240.0	1,500	6.2	0.41	4.5	11.0	Carcinoma of colon; intestinal obstruction	Gallbladder: cholesterosis, grade 1*

* On a basis of 1 to 4.

centimeter for the bile from the gallbladder. The ratio of cholesterol in the gallbladder bile to cholesterol in the hepatic bile fell between 4 and 36.1.

It may be seen in these three tables that the actual figures for each group are not so different from those of the others. They are differentiated by the fact that the two constituents studied are concentrated unequally in groups 2 and 3 and equally in group 1.

Simply as a matter of record, these figures may be added to the quantitative study of biliary physiology. They show that the hepatic bile may contain as little bilirubin as 96 mg. or as much as 1,720 mg. per hundred cubic centimeters. The gallbladder bilirubin may vary from 96 to 6,000 mg. per hundred cubic centimeters. The concentration of cholesterol may be from 0.25 to 13.3 mg. per cubic centimeter in the

hepatic bile and from 0.8 to 17.85 mg. per cubic centimeter in the gallbladder. The extreme variations in the hepatic bile point to great flexibility in the excreting power of the liver.

Similarly, the wide variation both in the actual figures for cholecystic bilirubin and amounts of cholesterol and in the ratios of concentration of bilirubin and cholesterol by the gallbladder speaks of a remarkable flexibility in function of the gallbladder.

COMMENT

These figures have their primary significance in adding to the quantitative studies of bilirubin and cholesterol determinations with more recent methods. They confirm previous studies in their wide range of value.

Secondarily, by having studied the bile from the liver and from the gallbladder simultaneously, we may correlate the quantities present and infer from these ratios something as to gallbladder function. It may be seen from the numbers of cases in each table that the preponderance of evidence is in favor of simple concentration of cholesterol by the gallbladder. Next, the evidence would favor the hypothesis that cholesterol is absorbed by the mucosa of the gallbladder.

Since only 4 of the cases fell into the group with higher concentrations of cholesterol, that is, indicating secretion of cholesterol by the gallbladder, it might be inferred that these instances are rare. However, the fact that there are cases which fall into all three groups is evidence for the contention of Wilkie and Doubilet [12] that the direction of the passage of cholesterol across the mucosa of the gallbladder depends on the relative concentration of this substance in the bile and in the blood.

The most profound objection to a study of this nature is that it is determining physiologic data on postmortem material Agonal and postmortem changes might profoundly influence the bile secreted by the liver or the bile already present in the gallbladder. As regards the latter possibility, Elman and Taussig [3a] maintained that after death the mucosa of the gallbladder desquamates rapidly and that high values are partly due to cellular debris. Doyon and Dufort [16] agreed with this statement. There is evidence from these sources that cellular desquamation may lead to increased cholesterol in the bile. Note, however, that in not one of these 4 cases was there marked cholesterosis, nor were cholesterol polyps present. Grossly, the conditions were comparable to those of the other two series.

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16. Doyon, M., and Dufourt, M.: Contribution à l'étude de la sécrétion biliaire; élimination de la cholestérine par la bile, Arch. de physiol. norm. et path. **8**:587-594, 1896.

Elton [4b] compared postoperative and postmortem bile and found that "The possible influence of dehydration, age, cause of death, and interval between death and necropsy were not demonstrable, and furthermore, gallbladder bile apparently undergoes a most excellent state of preservation in the intact viscus for at least forty-eight hours." He stated further, "No correlation between bile concentration and therapy or preagonal abstinence from food in prolonged illnesses could be determined."

As regards the possible agonal changes in cholesterol metabolism, Goff, Hrdina and Andrews [17] studied two series of dogs, in one of which the animals were killed and in the other of which they died, after ligation of the common duct. In the two series the average cholesterol content of the bile was the same, but in the dogs that died the bile salt content was 25 per cent lower. This study would indicate that there is no agonal change in hepatic secretion of cholesterol.

The contention that hepatic bile is not of constant composition and that the bile stored and concentrated by the gallbladder may originally have been of different composition from the hepatic bile studied post mortem seems unanswerable and is a formidable obstacle in drawing satisfactory conclusions from this study.

That the gallbladder is ideal anatomically for concentrating fluids is universally recognized. The degree to which it may concentrate is debated. Schöndube and Kalk [4f] expressed the opinion that it can concentrate bilirubin one hundred times; Newman,[4d] only five to forty times—an average of about twenty times. In dogs, Rous and McMaster [18] found a concentration factor of ten times for bilirubin. According to the figures in the present study, bilirubin concentration may reach twenty-four and one-half times the hepatic value in the gallbladder. The highest ratio for cholesterol was thirty-six and one-tenth times. If one uses the lowest figure obtained for hepatic bilirubin (ninety-six) and the highest for gallbladder bilirubin (six thousand), one may infer that under extreme conditions bilirubin might be concentrated as high as sixty times in the gallbladder.

SUMMARY

The present investigation demonstrates that sufficient bile can be removed post mortem from the extrahepatic biliary tree for a comparative study of hepatic and gallbladder bile. It adds a new group of quantitative determinations for both bilirubin and cholesterol from the gallbladder

17. Goff, M.; Hrdina, L., and Andrews, E.: Effect of Prolonged Stasis on the Bile Salt-Cholesterol Ratio, Proc. Soc. Exper. Biol. & Med. **29**:549-550 (Feb.) 1932.

18. Rous, P., and McMaster, P. D.: The Concentrating Activity of the Gall Bladder, J. Exper. Med. **34**:47-75 (July) 1921.

and common hepatic duct. It shows that there is a marked variation in these substances in the liver bile and in the concentrated gallbladder bile.

Comparative studies of the relative concentration of bilirubin and cholesterol by the gallbladder indicate that in the majority of instances (19 of 31) the cholesterol of the hepatic bile is simply concentrated pari passu with the concentration of bilirubin. However, 12 of the 31 cases studied do not fit in with this hypothesis, and evidence is given that in certain instances cholesterol may be either added to or removed from the gallbladder, as Wilkie and Doubilet [12] postulated.

REVIEW OF UROLOGIC SURGERY

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(Concluded from page 1304)

BLADDER

Hunner's Ulcer.—Rusche and Hager [48] presented some observations on the development of malignancy in Hunner's ulcer, and they reported 2 cases.

In 1 case the patient was a man aged 26 years, in whom definite Hunner's ulcer was found. Treatment consisted of the usual measures. Fifteen years later he was again examined. He was in a critical condition at this time and died shortly afterward. Cystoscopic examination had not been made. Microscopic examination of the wall of the bladder showed a definite carcinoma. The tumor was anaplastic, and a growth infiltrated the tissues. It resembled a scirrhous neoplasm, such as might have been found in the presence of gastric carcinoma.

In the second case the patient was a woman 65 years old who was seen in 1933, at which time several irregular portions 1 cm. in diameter had been seen in the posterior wall of the bladder during cystoscopic

48. Rusche, C., and Hager, B. H.: Further Observations on the Development of Malignancy in Hunner Ulcer, Tr. Am. A. Genito-Urin. Surgeons **32**:203-210, 1939.

examination. These portions were typical of interstitial cystitis. This patient was seen again three years later, at which time an extensive infiltrating neoplasm involving most of the surface of the bladder was found.

Of interest is the fact that there was no demonstrable evidence of metastasis in either case; in each the neoplasm seemed to be limited to the interior of the bladder.

Hagner,[49] in discussing Rusche and Hager's article on Hunner's ulcer, stated that he had reported on a woman whom he had had under observation for nearly three years. She was suffering from Hunner's ulcer. She had been at one time practically free from symptoms, and he had not seen her for about six months. She returned and said that she had experienced some amount of bleeding. A cystoscopic examination was made, and unquestionably there was a carcinoma, about the size of a thumbnail, situated at the top of her bladder. The patient died about six months later from general abdominal metastasis of the primary lesion.

Hagner stated that it used to be a great comfort to him to tell patients who had a solitary ulcer that such an ulcer practically never heals but that it never develops into a neoplasm. This statement cannot be made now. Hunner had reported only 1 case of such a transformation at the time Hagner reported his case, and, as far as Hagner knew, his case and Hunner's are the only 2 reported cases in which Hunner's ulcer has developed into a malignant neoplasm.

Sisk [50] pointed out the fact that sulfanilamide will benefit many patients who have old chronic Hunner's ulcer. He discussed the condition of 2 patients. One of these had been treated elsewhere for about five years and had been under Sisk's observation for about seven years. By means of sulfanilamide therapy she was almost entirely relieved of her symptoms and had remained so for a year at the time of Sisk's report. Another patient, who had a lesion of seven or eight years' standing, had been entirely free of pain for more than a year at the time Sisk spoke of her, although she still had frequency of micturition, urinating about once every two to three hours.

Tumor.—Colby [51] stated that evidence collected thus far gives little support to the contention that malignant tumors of the bladder can be cured by supervoltage irradiation. The method is recent, and the dosage

49. Hagner, F. R., in discussion on papers of Rusche and Hager and Sisk and Neu, Tr. Am. A. Genito-Urin. Surgeons **32**:212, 1939.

50. Sisk, I. R., in discussion on papers of Rusche and Hager and Sisk and Neu, Tr. Am. A. Genito-Urin. Surgeons **32**:212, 1939.

51. Colby, F. H.: Supervoltage Radiation in the Treatment of Bladder Tumors, Tr. Am. A. Genito-Urin. Surgeons **32**:225-231, 1939.

is still undetermined. In Colby's cases, the cancer seems to have been affected to a greater extent by supervoltage treatment than by other forms of external irradiation. Extensive tumors have regressed to the point of gross disappearance, but there is evidence that even in such a favorable event cancerous cells persist in the deep layers of the wall of the bladder. Although the intravesical portions of a tumor may disappear, it has been evident that large regions of cancerous tissue can persist in the deep structures, so that cancer will reappear in the bladder. Recurrent growths have responded less well to additional irradiation, and in no instance has the tumor disappeared again after more treatment. The most favorable responses were obtained with patients who had received no previous treatment. Colby's experience during the two years prior to his report caused him to feel that this treatment should be used only for patients who have advanced tumors or for old and debilitated patients and that any tumor of the bladder suitable for surgical treatment should be operated on.

Gayet [52] stated that leiomyosarcoma of the bladder is a form of tumor that has not been sufficiently brought to the attention of urologists. It is more common than is classically believed, has a rapid course and terminates fatally in four to six months after its clinical recognition. In addition to the symptoms that usually accompany cancer of the bladder, intense fetid and necrotic cystitis is present. The appearance of the lesion at the outset, when it is discovered, is that of a pedunculated and regular tumor, in contrast to the fulminating evolution which is the general characteristic of vesical tumors. Such pedunculation and regularity constitute a ready source of error in diagnosis.

Gayet observed within a few months 3 patients who had tumors of this kind. He presented the histories of these patients. Study of the literature reveals that leiomyosarcomas of the bladder are more common among men than among women and that, unlike most sarcomas, which attack the young, they have been observed to afflict patients who are mostly between the ages of 40 and 60 years, an observation which suggests that they possibly develop on the basis of a preexisting myoma. Some of them may be envisaged as the possible result of degeneration of a benign vesical tumor. Unquestionably, purely myomatous portions coexist with other portions that exhibit malignant degeneration. It is unfortunate that no case of benign leiomyoma has been published in which the transformation into sarcoma has actually been observed secondarily, although 1 of Gayet's cases suggests this eventuality.

The fundamental anatomic appearance of such a neoplasm reveals both of its constituents, muscular hypertrophy and degeneration of con-

52. Gayet, R.: Les léio-myo-sarcomes de la vessie, J. d'urol. **48**:320-333, 1940.

nective tissue. Three sites of election have been observed, as is the case when uterine myomas are present: (1) interstitial and extraparietal; (2) submucous, or cavitary, and (3) peripheral, or excentric. The point of implantation is most frequently the trigon, but the tumors have been found in the lateral walls and even in the dome of the bladder. The size and weight of these tumors are very variable, weights of 500 Gm. and 3 pounds (1.3 Kg.) having been reported. In 2 of Gayet's cases the entire bladder was invaded. The tumor may be pedunculated or sessile, or several pedicles may be twisted about a common axis. Necrosis is rapid because of deficient nutrition. Infection appears, which is carried rapidly to the kidneys. Nearby organs are seldom invaded, only 1 instance of metastasis (to the humerus) having been observed in 15 cases collected by Kretschmer.

Microscopically, leiomyosarcoma is characterized by cellular anarchy, the considerable size of each element and the presence of numerous mitoses, confirming the malignancy of the tumor. Clinically, the first signs are pollakiuria and sometimes marked dysuria, followed by capricious hematuria which appears on every attempt by the surgeon at exploration. In diagnosis, the most important signs are (1) the fetid urine filled with debris and (2) the cytoscopic appearance, which is clearly that of cancer when the mass is of the type of an infiltrated tumor (when, however, it is rounded and regular, resembling a myoma, error is more likely to occur). Only biopsy insures a certain diagnosis, revealing an association of hypertrophied muscle fibers and sarcomatous cells.

Many urologists regard such a condition as too hopeless for treatment. Others have tried the various form of irradiation and surgical treatment, none of which, however, have proved to be more than palliative. Cystostomy, although it permits partial evacuation of urine and debris, often causes exacerbation instead of relief of pains; it also hastens the spread of the malignant neoplasm. Cystectomy, whether total or partial, fails. It has been followed by rapid recidivation and death in all the author's cases. The extreme malignancy of these tumors does not encourage the surgeon to attempt their removal.

Exstrophy.—Godard [53] applied a form of technic somewhat different from the usual approach in 2 cases of exstrophy of the bladder and in 1 of epispadias. Having observed the difficulty involved in closing the bladder if care is not taken to mobilize it widely and to bring it down as low as possible in the pelvis, he decided on prerectal pelvic transposition of the bladder. The method is not applicable to female patients, because of the anatomic position of the bladder in females, and should

53. Godard, H.: L'exstrophie vésicale et l'épispadias masculine, leur traitement par la transposition pelvienne pré-rectale de la vessie, J. d'urol. **47**:97-109 (Feb.) 1939.

not be tried in boys until they are 5 or 6 years of age, because of the narrowness of the bony pelvis in such patients.

The technic has two principal aims: (1) invagination of the bladder and its reconstitution as a reservoir for the urine and (2) reposition of the bladder within the pelvis, with a view either to its control by the anal sphincter or to later reconstruction of the urinary passages to a nearly normal state by Marion's plastic transfixing operation.

The genital system (penis and prostate gland) is left in place in the pubic region, the urinary system having become pelvic (analogous to an embryonic cloaca), or being drained temporarily by way of the perineum until such time as urethroplasty is done. The technic is briefly as follows:

In the first stage the patient is placed in the horizontal position, and two ureteral catheters are used to drain the urine from the operative field, while the bladder is kept invaginated by a pack of compresses. After a traction thread of silk has been placed around the neck of the bladder, a racket-form incision is made; it passes as nearly as possible to the bottom of the urethrovesical furrow, which often can be recognized behind the verumontanum. In the second stage the globe of the bladder is freed, and the peritoneum is cautiously separated from its postero-superior surface. In front this dissection is rather laborious, for here and there is a vascular pedicle that must be tied. The dissection proceeds downward, forward and slightly to the side without any difficulty. The bladder is then progressively sunk down into the pelvis, where the silk thread will at once permit fixation of it.

After incision of the skin at the anterior margin of the anus, the outermost fibers of the anal sphincter are split, a wide band of internal sphincter being left intact. In carrying out the dissection the pelvis is entered, and the vesical silk traction threads are picked up.

This stage is somewhat difficult, since traction has to be made not only on the vesical orifice but on the catheters; a competent assistant is required to keep an eye on the abdominal part of the operative field and to facilitate the maneuvers. The vesical tamponade is removed, care being taken to maintain in place the ureteral sounds, which are left in position for several days or, better, are replaced by a Pezzer catheter, firmly fixed.

The operation ends with partial closure of the abdominal incision, partial closure frequently being all that can be done, because of lack of available skin and muscle for complete closure. Drains are placed in the incision, and gauze is inserted to fill up the dead spaces.

After what is usually a long process of cicatrization, the new orifice appears in front of the anus, from which it is separated by a sort of spur resembling a swollen hemorrhoid.

Four patients have been treated by this method, and the procedure has been followed later by operation for epispadias. Esthetic results have been excellent, and the degree of continence obtained, although not perfect, has been remarkable. The technic can and should be further improved. Since children born with these deformities commonly exhibit mental deficiency as well, it is hardly likely that any of them can ever urinate normally.

Diverticula.—Radical complete diverticulectomy is often a difficult and dangerous procedure. Barnes [54] described a technic for the successful obliteration of large vesical diverticula which cause residual urinary and vesical symptoms. This procedure utilizes a combination of the intravesical and extravesical approaches and provides adequate exposure of the interior of the diverticulum, so that the mucosa can be removed by stripping or by cauterization. The diverticular orifice and the incisions through the wall of the bladder are sutured with no. 000 chromic catgut in two layers, a muscular and a submucosal layer, and the diverticular cavity is treated with an antiseptic solution and drained extravesically. Shock and postoperative perivesical sepsis are reduced to a minimum by this technic, and there has been no persistence or recurrence of the diverticulum.

Thompson, Kermott and Cabot [55] pointed out the fact that diverticula contain all the coats of the bladder and are truly congenital in origin but become symptomatic later in life because of obstruction of the vesical neck. Various plans of treatment have been devised, such as (1) two stage suprapubic prostatectomy and diverticulectomy, either in the order given or in reverse order; (2) a one stage operation, and (3) transurethral prostatic resection with or without subsequent diverticulectomy.

These authors studied 14 patients who had vesical diverticula and who were treated only by means of suprapubic prostatectomy. None at the end of a two year follow-up study needed diverticulectomy, yet most had had a long and complicated convalescence. Secondary diverticulectomy is a much more serious operation in such cases than the primary operation for diverticulum would have been.

Ninety-six patients who had vesical diverticula and who were treated by transurethral resection also were reported on. The diverticula varied in size from small (24 cases) to large, that is, equivalent in size to the bladder (17 cases). The postoperative course was short, smooth and uncomplicated. All the patients were almost completely relieved of

54. Barnes, R. W.: Surgical Treatment of Large Vesical Diverticula: Presentation of a New Technique, J. Urol. **42**:794-814 (Nov.) 1939.

55. Thompson, G. J.; Kermott, L. H., and Cabot, H.: The Management of Diverticulum of the Bladder: Ninety-Six Patients Treated by Transurethral Prostatic Resection, Surg., Gynec. & Obst. **70**:115-119 (Jan.) 1940.

their symptoms by the surgical treatment. Subsequent diverticulectomy has not been necessary, but if it should be necessary, it ought to be a comparatively simple primary procedure. Diverticulectomy now is done only a third as many times at the Mayo Clinic as formerly, a fact which tends to demonstrate the satisfactory results which can be obtained from transurethral resection. Of follow-up study the 96 patients mentioned revealed that they enjoyed satisfactory results as to both symptoms and amount of residual urine present.

Diverticulectomy is indicated (1) when the diverticulum does not drain adequately through a small orifice; (2) for young men, who have poor drainage after resection; (3) when stone or carcinoma is present in the diverticulum, and (4) when ureteral obstruction is present.

Regeneration.—Sisk and Neu [56] reported a case of regeneration of the bladder. The patient was a man 56 years old. At operation a large carcinoma was found to extend across the dome of the bladder. Since this portion of the tumor had not invaded the perivesical tissues, the operation was continued in the hope that it might be possible to resect the tumor. The peritoneum having been dissected free, the bladder was opened behind the region involved by the tumor. As exploration of the bladder proceeded, it was found that the tumor completely encircled the neck of the bladder. The entire bladder was removed with the exception of a small portion of the posterior wall, which measured about 3 by 3 cm. The ureters were cut across, and, since it was found that the tumor had invaded to some extent the right lobe of the prostate gland, a number of radium emanation seeds were introduced into this region. When the operation had progressed to this point, the patient exhibited definite evidence of shock. Drains were introduced into the bed from which the bladder had been removed, and the incision was closed in layers. The patient was seen four months later. Shortly after returning for consultation he began to void urine through the urethra. The incision had healed completely. He was at this time voiding about every two hours. The suprapubic incision was well healed. A cystogram permitted the introduction of 3 to 4 fluidounces (88 to 118 cc.) of medium. The fundus of the bladder appeared to be smooth and regular in outline. The patient died some months later.

Sisk and Neu stated that in spite of the fact that permission to do necropsy was not obtained and that there was no definite knowledge of the actual degree of regeneration of the bladder, it was clear that within about two and a half months after removal of all except a small segment of the posterior wall of the bladder a cavity developed which solved the problem wholly and suitably.

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56. Sisk, I. R., and Neu, V. F.: Regeneration of the Bladder: Report of a Case, Tr. Am. A. Genito-Urin. Surgeons **32**:197-202, 1939.

Neurogenic Disease of the Bladder.—Nesbit and Gordon [57] stated that uninhibited neurogenic disease of the bladder is a clinical syndrome characterized by frequency of urination, nocturia and imperative micturition. The causative lesion is situated in the central nervous system and not in the lower part of the urinary tract. Differential diagnosis must be made to distinguish uninhibited neurogenic disease of the bladder from irritative lesions of the urinary tract, such as infection and early prostatism. Drug therapy is the only available form of treatment at present. The drug of choice is tincture of belladonna. Beneficial results were obtained in 9 of 16 cases in which the patients were treated with this drug. Twenty-five cases were reported in detail.

Cystitis Associated with Osteomyelitis.—Mathé [58] reported 3 cases of long-standing intractable cystitis secondary to chronic osteomyelitis of the pubic bone, a late complication of fracture of the pelvis and rupture of the bladder. In all 3 cases the patients were relieved by operation.

Three types of chronic cystitis are observed: (1) that resulting from traumatic rupture of the bladder, associated with fracture of the pelvis or luxation of the pelvic bones; (2) that caused by osteomyelitis of the symphysis and rami of the pubis occurring after operations on the bladder or by osteomyelitis of the pelvic girdle following operations on its component bones, and (3) cystitis referable to nontuberculous hematogenous osteomyelitis of the pubis and thigh, which usually occurs during childhood.

Chronic urinary infection associated with hematogenous and traumatic osteomyelitis of the pelvic girdle is the result of complicating infected sequestrums, involucrums, abscesses, spontaneous rupture of the bladder and osteovesical fistulas.

The condition should be suspected when patients present chronic pyuria with which there is a history of previous fracture of the pelvis or of attacks of osteomyelitis during childhood. Rectal and vaginal palpation enables the examiner to detect distended portions in the bones making up the pubic arch; such distention is referable to sequestrums, abscesses and fistulous tracts. Cystoscopic examination enables the urologist to visualize migratory fragments of bone and sequestrums, associated stones and the openings of fistulous tracts. Roentgen examination of the pelvic girdle demonstrates regions of rarefaction and fraying

57. Nesbit, R. M., and Gordon, W. G.: The Uninhibited Neurogenic Bladder: A Clinical Syndrome with Report of Twenty-Five Cases, Tr. Am. A. Genito-Urin. Surgeons **32**:213-224, 1939.

58. Mathé, C. P.: Management of Intractable Cystitis Associated with Vesical Fistula and Osteomyelitis of Pelvic Girdle: Report of Three Cases Following Traumatic Rupture of the Bladder and Fractured Pelvis, J. Urol. **43**:543-560 (April) 1940.

of bone margins caused by osteomyelitis and periostitis. Cystograms show distortion of the bladder and displacement as well as communicating osteovesical fistulas.

Prophylactic treatment consists of hermetic diversion of the urinary stream by suture of the wall of the bladder to the skin at the time of original surgical intervention for rupture of the bladder. Surgical treatment consists of sequestrectomy, curettage of infected bone, débridement of infected surrounding tissues, removal of connecting fistulous tracts and drainage of contiguous abscesses in conjunction with cystotomy or drainage by catheter.

Incontinence.—Influenced by the excellent results obtained by Cathelin in the treatment of idiopathic and infantile incontinence of the urinary bladder by epidural injections of solution of sodium chloride, Marti [59] tried this method of treatment for incontinence caused by insufficient control of the sphincter. He injected 20 to 30 cc. of a 2 per cent solution of sodium chloride into the sacral canal at weekly intervals. He never made more than six injections, and it was never necessary to hospitalize a patient. Marti tried this method in 17 cases, in 16 of which he obtained satisfactory results.

Fistula.—O'Conor [60] reported on 4 patients who had vesicovaginal fistulas who were cured by cystoscopic and vaginal electrocoagulation after attempts at surgical repair had failed.

Healing is aided by the insertion of an indwelling urethral catheter and placement of the patient in a posture which is suitable for keeping the fistulous region as dry as possible. The hydrogen ion concentration of the urine should be kept at 5.5 or less by the use of the acid ash diet and ammonium nitrate to prevent incrustation of the coagulated tissue and deposition of lime in the catheter.

This method is not indicated in the treatment of fistulas involving the floor of the bladder or in cases in which there are extensive defects in tissue but should receive more consideration than it has received in the past, especially when unsuccessful surgical repair has resulted in formation of a small lateral opening.

Contracture of Vesical Neck.—Thévenard [61] discussed the clinical picture and treatment of diseases of the neck of the bladder in women. The principal signs are those of obstruction to the outflow of urine, which causes first progressive dysuria, then pollakiuria and, if retention is of high degree, a sensation of weight in the hypogastrium. Simul-

59. Marti, T.: Zur Behandlung der durch ungenügenden Sphinkterschluss bedingten Harninkontinenz der Frauen, Ztschr. f. Urol. **33**:692-696, 1939.

60. O'Conor, V. J.: Non-Surgical Closure of Vesicovaginal Fistula, Surg., Gynec. & Obst. **70**:826-827 (April) 1940.

61. Thévenard, P.: La maladie du col vésical chez la femme, J. d'urol. **48**: 296-319, 1940.

taneously, the usual signs of intoxication appear, chief among which is uremia, indicating repercussion on the renal function; finally, there is dilatation of the pelves and ureters, with bilateral hydronephrosis, which grows constantly worse until incontinence appears as the last stage of the condition. Not all these signs are necessarily present in any given case. Other conditions which appear are congestion, spasm and infections; among these the most frequent is cystitis, which causes a burning sensation and frequency of urination. What are at first temporary attacks tend to become permanent; they may lead to bleeding of the vesical mucosa and then to bullous edema and the appearance of inflammatory new growths. As these progress, the capacity of the bladder shrinks. Dynamic disturbances set up by the infection aid in the development of ureteropyelitis and pyelonephritis of varying acuteness. Two special complications may then develop, namely, diverticulum of the bladder and vesical lithiasis.

In diagnosis, the chief points to consider are the history of the patient and the results of cystoscopic examination. An early and constant indirect sign is the existence of columnar formation, an occurrence which attests to the struggle of the vesical muscles against the obstruction at the neck of the bladder. Less constant are such signs as modification of the neck of the bladder evidenced by thickening of the sphincter, irregularity of the orifice and various deformations. Urethroscopic examination, however, shows nothing that can be called absolutely characteristic.

The only form of radical treatment is resection of the neck of the bladder, which may be carried out by the high transvesical method, with scissors (Marion's method), or transurethrally by high frequency current. The first procedure is now seldom used, being suitable only in exceptional cases in which endoscopic resection has failed or when cystostomy is required for other, concomitant conditions.

The type of instrument chosen for application of high frequency current may be any one of those in common use for endoscopic prostatic resection, and the instrument is of less importance than the surgeon's judgment of just how much tissue to resect. The danger of production of incontinence, which was real in the past, now practically does not exist in the hands of an experienced urologic surgeon. In an occasional case temporary incontinence may occur and may last a few weeks or months, but it almost invariably disappears with the passage of time. The best approach to the neck of the bladder appears to be the circumferential route, which requires the least penetration for removal of a given amount of tissue. This mode of approach smooths out all irregularities and leaves the vesical neck perfectly circular; often the procedure can be accomplished at a single operation, after which a retention catheter is inserted, left in place for from two to four days and not

removed until the urine is clear of blood. As a rule no further treatment is needed, but for an occasional elderly patient dilations may be needed because of the sclerotic changes caused by advancing age.

Emmett [62] stated that obstruction of the urethra in infant boys usually is suspected because of the appearance of symptoms of urinary infection, such as fever, urgency and frequency of urination and painful urination as demonstrated by the infant's crying during micturition.

He reported a case in which a boy aged 18 months had urinary difficulties. Micturition was frequent and was accompanied by straining. This trouble had increased gradually in severity until, at the time of admission, the father said that the child "strained like an old man to urinate." At each micturition the child cried.

Cystoscopic examination was carried out with the infant under anesthesia produced by nitrogen monoxide. Only a moderate amount of urine was present in the bladder, some of which may have been residuary. The bladder, ureteral orifices and vesical neck appeared to be normal. On withdrawal of the cystoscope into the prostatic portion of the urethra an abnormally large verumontanum was encountered, which was of sufficient size to occlude the urethra almost completely. Careful examination of this structure failed to disclose any definite cystic formation. The hypertrophied verumontanum was fulgurated by means of an electrode through the cystoscope.

The results of fulguration were excellent. The patient was dismissed three days after fulguration, at which time he did not strain on voiding and the urinary stream was normal. He still cried during micturition, evidently because of irritation resulting from fulguration. Six weeks later he apparently had completely recovered, since he voided normally without discomfort and the urine was clear.

TESTIS

Tumor.—Gilbert [63] summarized data concerning 126 small tumors of the testis. Of approximately 7,000 malignant tumors of the testis, only 126 (1.5 per cent) were situated in testes of normal or smaller than normal size. Of these, 118 were finally diagnosed accurately, although 11 were diagnosed only at necropsy.

The age of 113 patients averaged 32.3 years. In 48 cases the tumors affected the right testis; in 35 they affected the left testis, and in 2 they were bilateral (scrotal). Alleged trauma occurred in 15 cases (12 per

62. Emmett, J. L.: Obstruction of the Vesical Neck of a Male Infant Produced by Hypertrophy of the Verumontanum: Report of Case, Proc. Staff Meet., Mayo Clin. **15**:364-365 (June 5) 1940.

63. Gilbert, J. B.: Studies in Malignant Tumors of the Testis: I. Differential Diagnosis of Clinically Obscure Tumors; Four Cases and Review of One Hundred and Twenty-Two from the Literature, J. Urol. **43**:722-733 (May) 1940.

cent) and appeared to be an important factor in the early removal of small tumors, even though the correct clinical diagnosis was not made.

There were 46 (36.5 per cent) unicellular and 71 (56.3 per cent) teratoid tumors (29 teratomas and 42 chorionepitheliomas).

Scrotal disease was evident on first examination in only 59 patients (47 per cent). Of these 59 patients, 32 were considered to have testicular tumors, whereas all other possible scrotal conditions were diagnosed in the cases of the remaining 27 patients. In 26 cases abdominal metastases were mistaken for intra-abdominal disorders, although only 16 of these were considered to be tumors. In the remaining 41 cases the patients were considered to have primary disease of the thorax, the head, the neck and even the extremities. Hormonal assays aided in formation of the correct diagnosis in 21 of 53 cases in which the patients were seen after 1932. Assays in which the results were positive also were made concerning 10 of 18 patients who had gynecomastia. In 2 instances repeated assays in which results were negative were consistent with clinical cures of respectively four and five years' duration.

Orchidectomy was performed on 67 patients, in 24 instances in the presence of metastases. Fifty-nine patients were considered to be inoperable. Five radical operations were performed. Irradiation therapy was applied to 40 patients; this number included 2 patients who received radium therapy.

Only 12 patients survived for five years or more (10 had unicellular tumors, and 2 had teratomas). Of the 10 patients who had seminomas, 2 died after periods varying between five and ten years; 8 patients were known to have survived.

Wesson [64] expressed doubt that tumors of the testicle are rare. Only those tumors have been reported which caused real trouble and brought the patients to urologists for treatment or caused them to apply for hospitalization, and because of this, only a few tumors have been reported. On the other hand, many men who have nonmetastasizing tumors live for the normal span of life and die of intercurrent infections, oblivious to the fact that they have been harboring an "inactive" cancer. Char, of the Peiping Union Medical College, wrote that in eighteen years he had seen 34 patients who had such tumors. The tumors were said to have been present for from six months to fifty years. Nineteen of them were of more than two years' duration.

Trauma usually is considered to be a probable predisposing factor in the causation of tumor, but Wesson believed that it is of no significance. At best, trauma is an eagerly remembered coincidence. A history of trauma always should be ignored unless the blow was adequate to produce some structural alteration visible to the naked eye, such as

64. Wesson, M. B.: Tumors of the Testicle: Report of Some Unusual Cases, Tr. Am. A. Genito-Urin. Surgeons **32**:347-358, 1939.

ecchymosis. Ewing, after a very comprehensive investigation of the literature and careful study of many cases of tumors of the testicle which were alleged to have been traumatic in origin, concluded that data now at hand confirm the view, long since adopted by pathologists, that single traumatization of normal tissues is incapable of producing a malignant tumor. His contention was that in a given case the growth was present and the trauma was merely a coincidence eagerly remembered by the patient.

The presence of a teratoma is unknown to a patient afflicted with it until it becomes sufficiently large to manifest itself subjectively or objectively. Frequently the pain or tumor is first noticed after slight strain or trauma, and, consequently, strain or trauma is assumed to be responsible for a condition that has long been present but has just progressed to active growth.

Orchidectomy supplemented by ample high voltage roentgen therapy is the procedure of choice.

Barringer,[65] in discussing Wesson's article on tumors of the testicle, stated that Ewing recently had given him the history of a patient whose entire course of life, from the time of appearance of the first symptom to death, was much shorter than the life of any of the patients in the cases reported by Wesson. In Barringer's case the life of the patient was a matter of several weeks.

The question of metastasis in these cases is very interesting. Barringer had given, a year prior to the time of his discussion, expert testimony concerning the supposition that if a man had lived five years without metastasis he could be considered a fit candidate for life insurance. During the next month he saw 2 patients who had been afflicted by metastasis five years after operation. The condition of 1 patient was interesting. He had had a teratoma of the testis treated originally at the Memorial Hospital in New York city, and he had lived for nearly six years thereafter without experiencing any symptoms. Finally a tumor had developed to the left of the thyroid gland, accompanied by intense dyspnea. The local surgeon wished to perform a tracheotomy, when the patient suddenly remembered that he had had a teratoma of the testis. Barringer aspirated the supraclavicular mass, and Ewing, in about five minutes, gave Barringer the diagnosis of metastasis from the primary lesion. Roentgenograms were made, and after about seven years (at the time of Barringer's discussion) the patient was still well. This case shows the value of aspiration of a specimen of tissue for biopsy.

Wesson apparently administered roentgen therapy after the operation on his patients. Barringer thought it reasonable to administer roentgen treatment before operation on the testicle. By virtue of moder-

65. Barringer, B. S., in discussion on papers of McKenzie, Culver, Wesson and Graves and Flo, Tr. Am. A. Genito-Urin. Surgeons **32**:386, 1939.

ate roentgen therapy to the testicle, he thought, several things could be accomplished: The testicle itself would have the benefits of preoperative roentgen therapy and would present the appearance of a good pathologic specimen, and the cells of the neoplasm, which are the most highly malignant cells recognized in any tumor occurring in the human body, would be devitalized before operation on the testicle.

Hagner [66] stated that he had only a moderate experience in the treatment of tumors of the testicle and that he had never believed that he could say much about them. The urologist sees some patients who have lived for years and others who die in a few months, and yet the pathologic reports may not be dissimilar. Hinman advised roentgen therapy after removal of the testicle, claiming that the surgeon cannot determine definitely the nature of cellular elements if the tumors have been submitted to preoperative roentgen therapy; Hagner, conversely, expressed the belief that roentgen therapy should be administered before the testicles are operated on.

In 1 of Hagner's cases a patient who had a seminoma, apparently of a rather malignant type, received roentgen therapy before the tumor was removed. The testicle was almost normal in size when it was taken out; it had regressed very much, and the patient made a good recovery. He remained perfectly well for nine years; then a tumor developed in his neck, and he came back to Hagner. By that time the Aschheim-Zondek test had been developed; the patient was tested, and the reaction was found to be positive. The patient received roentgen therapy, and the tumor literally "melted away" from his neck. Within a year, a tumor almost the size of an orange developed in the midline in his abdomen, evidently in the mediastinal glands. The reaction to the Aschheim-Zondek test had become negative after the tumor in the patient's neck had disappeared, and when he returned a year later with the tumor in his abdomen the reaction to the Aschheim-Zondek test was positive. That tumor was treated, and it disappeared. Although the reaction to the Aschheim-Zondek test became absolutely negative at that time, the patient had been apparently well for about a year and a half at the time of Hagner's remarks. This is an interesting case from the standpoint that the patient had lived for nine years, apparently well, before he had a recurrence of probably the same type of tumor that originally had appeared in the testicle.

Dean [67] stated that in Wesson's paper on testicular tumors Wesson had emphasized three points, namely, incidence, trauma as a causative agent and treatment.

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66. Hagner, F. R., in discussion on papers of McKenzie, Culver, Wesson and Graves and Flo, Tr. Am. A. Genito-Urin. Surgeons **32**:386-387, 1939.

67. Dean, A. L., Jr., in discussion on papers of McKenzie, Culver, Wesson and Graves and Flo, Tr. Am. A. Genito-Urin. Surgeons **32**:389-390, 1939.

Concerning incidence, Dean said, at the Memorial Hospital in New York city teratomas of the testes comprise 3.4 per cent of all tumors of the genitourinary system, 2 per cent of all malignant tumors occurring in male patients and 1 per cent of all malignant tumors occurring in both sexes. These figures correspond roughly to a frequency of from 1 to 3 per cent of all malignant tumors found by other investigators.

In Dean's experience, teratomas have been seen nearly twice as frequently as cancers of the penis. That these figures may vary widely in different institutions is shown by the fact that Char, of Pekin, China, said that in a year he operated on 200 patients with penile cancer, whereas at the Memorial Hospital only about 20 new instances of penile cancer are encountered within the same length of time.

Dean considered trauma to be a causative factor in the production of such tumors. If it is true that teratomas arise from misplaced sex cells, it would be difficult to attribute much importance to trauma as a causative agent, but, on the other hand, Wesson has not exaggerated the medicolegal importance of this problem, since in medicolegal cases trauma is usually alleged to be a factor. However, tumors are discovered so frequently after an injury to the testes has occurred that any possible relation between trauma and the development of these tumors should be studied. Tissue in testicular tumor is denser and heavier than normal testicular tissue. Dean expressed the belief that the added weight of the tumor causes the testis to hang lower and prevents the normal reflexes, which ordinarily lift the testis to protect it from threatened injury, from functioning so efficiently as these reflexes would act if no tumor were present. Thus, a testis which is the seat of tumor is more likely to be traumatized than is a normal testis. The injury draws the attention of the patient to the testis, and, in turn, a tumor is discovered by the physician. It is sometimes very difficult to explain to a jury why an injury cannot hasten the dissemination of a tumor admittedly present at the time of injury.

In most clinics, irradiation is of recognized value in the treatment of testicular teratomas, but there are still differences of opinion as to the best procedure to employ. Hinman is said to remove the testis without preoperative therapy, so that he may study its structure and make hormonal assays. Dean said that preoperative irradiation offers advantages because five year end results show a rate of survival 35.7 per cent greater for patients who have received roentgen therapy before undergoing orchidectomy than for patients who have been operated on first and have then received roentgen therapy as soon as the diagnosis has been made. In neither group were metastases demonstrable at the time of operation.

Interpretation of the results of histologic examination of a tumor after irradiation is largely a question of the training of the pathologist.

There are so-called ghost cells which are recognizable as devitalized tumor cells.

There seems to be agreement concerning the question of irradiation of the lymphatic pathway through the pelvis and abdomen to the epigastrium in all cases, whether or not metastases can be found. When this treatment is administered, the anterior and posterior portals are treated with fractionated doses carried to as high a total dose as possible. In this way a single cycle may be sufficient.

Of all Dean's patients who had teratoma (there were between 500 and 600 with teratoma of the testis), 29 per cent were without evidence of disease at the end of five years. Seventy-two per cent had had metastasis at the time of treatment. Considering only a smaller group, members of which were considered to be "primary operable" patients who had testicular tumors without evidence of metastases, the five year survival rate for the group was 78 per cent.

PENIS

Priapism.—Dawson [68] reported 5 cases of true priapism. Four patients recovered after treatment by multiple aspiration of the corpora cavernosa. Two of the 4 had sickle cell anemia. Sickle cell anemia has not been reported heretofore as associated with priapism. The part this associated factor plays in priapism is not known or discussed. The fifth patient died after the penis became gangrenous and was amputated and after urinary extravasation had occurred. Dawson noted that heat as a local agent is better than cold.

URETHRA

Calculi.—Culver [69] discussed primary posterior urethral calculi. The old literature abounds with reports of urethral calculi, and the majority of such reports deal with calculi of the anterior segments of the urethra. Englisch, reviewing 405 cases of impacted urethral calculi without regard to primary or secondary types, found that 58 per cent of the calculi were situated in the anterior portion of the urethra and 42 per cent in the posterior segment. In approximately one third of all recorded cases of posterior urethral calculi the stones are multiple, varying in number, size and contour according to their chemical content and the space within which they are confined.

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68. Dawson, G. R., Jr.: Priapism: Report of Five Cases, Two Cases Occurring with Sickle Cell Anemia, J. Urol. **42**:821-828 (Nov.) 1939.

69. Culver, H.: Primary Posterior Urethral Calculi, Tr. Am. A. Genito-Urin. Surgeons **32**:337-346, 1939.

All the 7 patients reported on by Culver, who ranged in age from 16 to 65 years, had definite prostatic bars and long-standing histories of urinary disorders, caused in the beginning by bars of either the congenital or the acquired type. The topography of the posterior part of the urethra in the presence of a bar facilitates retention of urine between the bar and the external urethral sphincter. If the constitutional factors necessary to the formation of stone are also present, the picture would seem to be complete for the beginning and progression of these calculi.

Establishment of the diagnosis of urethral calculi is usually definite and complete when the long-standing history is considered and when posterior urethral obstruction is encountered with a metal instrument. In most patients the instrument cannot be passed into the bladder, but the diagnostic metallic click which is heard is sufficient. Rectal examination likewise reveals observations absolutely diagnostic. The rounded, hard midline projection, sometimes fixed, sometimes movable, with crepitus, associated with multiple stones should not be difficult of correct interpretation.

Roentgen examination confirms the diagnosis with adult persons, but may be of no value with children, in whom uric acid or urates may be the only constituent of the stones. Roentgenograms should be made from both the anteroposterior and the semilateral position to determine the size, extent and number of the calculi present. Urethrograms contribute to the diagnosis because they permit visualization of complications, such as diverticula of the urethra or of the bladder.

Calculi in this situation, if they were small enough, possibly could be removed with forceps, and such a procedure frequently is used when secondary stones are present and the patient has had recent acute symptoms, but removal of stones of the primary type which have caused long-standing symptoms should not be attempted by this method.

The perineal approach, in which Young's prostatectomy exposure is utilized, has been used, but it has the technical difficulty of revision of the vesical neck, which is an important feature of a complete operation; it likewise requires for traction a urethra patent in the prostatic region, a condition which is not frequently present.

The suprapubic approach has been ideal for all patients in Culver's experience because it allows bimanual extrusion of the stone into the bladder, which is done by insertion of the surgeon's finger into the patient's rectum. Even with this help from below, the surgeon occasionally is forced to cut the vesical neck to accomplish his purpose. After the stone has been removed, it is a simple procedure, under vision, to remove the obstructing tissue of the vesical neck with either an electric loop or a suprapubic cold punch.

Postoperative management of the patient obviously consists of dilation of the posterior part of the urethra and careful attention to the prevention of infection of the urinary and genital tracts. Attention to distant foci of infection as well as to dietary and medicinal management for the purpose of preventing recurrence has its place in the treatment of patients with this type of stone, just as it has a place in the management of patients with any other type of urinary calculus.

Urethritis.—Spence [70] discussed a series of cases in which granular urethritis was present in women. In approximately one third of the cases a considerable degree of pyuria may be expected to be present. He expressed the belief that granular urethritis often will be found to be the cause of cystitis. If instances of bullous edema of the trigon, trabeculation and cystitis cystica were excluded, it would be found that cystoscopic examination disclosed acute or subacute cystitis to be present in 25 per cent of Spence's cases.

Gross hematuria, usually in the form of small clots appearing toward the end of micturition, was present in 9.5 per cent of the cases and justifies the inclusion of granular urethritis in a prominent position in the list of causes of blood in the urine of the female patient.

Polypoid and cystic masses were found in the unexpectedly high portion of 61 per cent of Spence's cases. It was Spence's impression that this figure, which is much higher than that usually given, is the result in part of his consistent use of foroblique instruments for scrutinizing the entire urethra, a procedure which enables him to detect many lesions which were overlooked previously, when he used right angle lenses.

Extensive light fulguration of the entire urethral lining has yielded more permanent symptomatic results and more instances of satisfactory late visual appearance of the urethra than were possible before.

Disturbances of the female urethra occurring during childhood parallel exactly similar disturbances in adult patients. The management of the patient is similar.

Stricture.—Alken and Zumach [71] are of the opinion that a preliminary urethrogram should be made in all cases of urethral stricture before clinical treatment is carried out. In the average case Alken and Zumach's treatment of the patient is similar to the treatment used in the United States, in that they use increasingly enlarged catheters and

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70. Spence, H. M.: Granular Urethritis in Women, J. Urol. **43**:199-203 (Jan.) 1940.

71. Alken, C. E., and Zumach, E.: Die klinische Behandlung der Harnröhrenstriktur. Ztschr. f. Urol. **33**:498-510, 1939.

sounds for dilation. They still perform internal urethrotomy for severe contractures, but they do internal urethrotomy only after they have performed suprapubic cystostomy.

SCROTUM

Carcinoma.—In discussing the treatment of carcinoma of the scrotum, Graves and Flo [72] stated that irradiation should not be relied on for the destruction of this tumor. The metastatic process in the groin seems stubbornly resistant to roentgen therapy, and the thin scrotal wall, which is almost lacking in normal tissue defenses beneath the primary growth, offers a poor field for the use of either radium or roentgen rays.

Basing their surgical methods solely on anatomic considerations, the authors wrote that it might be necessary to advocate complete removal of the entire scrotum, together with the skin of the base of the penis and the nodes of the groins en bloc, because this is a lymph-borne disease and because, as has been shown, there is an unusually free communication among the lymphatic vessels of this region. Fortunately, pathologic and clinical evidence suggests that less drastic procedures may be safe. The lymphatic-embolic mode of dissemination of this particular type of cancer renders it futile, probably, for the surgeon to attempt to remove the intervening channels between the tumor and the glands, and further support of this view is found in the fact that Graves and Flo have seen no instance of local recurrence of this tumor in the scrotum after adequate local excision has been performed, even in their series in which there was eventually a high mortality rate. The involved portion of the scrotum must be excised completely, together with a wide margin of surrounding normal scrotal wall. Undoubtedly, some degree of direct permeation occurs along lymphatic vessels in the immediate vicinity of the tumor. When the lesion lies near the median line, dissection should extend well on the opposite side, for the raphe has no significance so far as the lymphatic vessels are concerned, and the pathways of these vessels are continuous from one side to the other. Electrosurgical handling is desirable in these operations on the scrotum, because it aids in the control of hemorrhage.

Graves and Flo wrote that they sacrifice the testicle and divide the spermatic cord well above the external inguinal ring, at least on the side affected by the tumor. There is no lymphatic communication between the scrotum and the testis or its tunica, but closure of the remaining portion of the scrotum will be difficult in most cases if both gonads are spared and if more extensive excision is performed may be impossible unless both gonads are removed.

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72. Graves, R. C., and Flo, S.: Carcinoma of the Scrotum, J. Urol. **43**:309-332 (Feb.) 1940.

Both groins must be dissected. On the side on which the tumor is situated the incision that surrounds the neoplasm may be continued upward and outward, a little above and parallel to Poupart's ligament, to within 2 cm. of the anterior superior spine of the ilium. Then it should curve widely downward and inward across the lowest level of the femoral triangle. By turning medially the resulting broad-based flap of skin, the surgeon may gain ready access to the inguinal and femoral regions, so that all of the gland-bearing tissues may be removed en bloc, with the tumor, testis and cord. Another plan that may be used continues the scrotal incision upward and outward only until the incision communicates with an incision in the groin which curves in the other direction, beginning near the anterior superior spine, extending above Poupart's ligament to the spine of the pubis and then curving widely downward and outward across the lower portion of the femoral region. The flap is dissected laterally so that access to the gland-bearing region can be secured. In dissection of the groin in recent years Graves and Flo have employed these curved incisions in an effort to avoid as much as possible the sharp corners and acute angles which have seemed in the past to invite necrosis.

Every radical dissection of the groin in cases of scrotal cancer must be carried out with meticulous attention to the anatomic aspects of the lymphatic vessels as described previously.

HYDROCELE

Young [73] stated that the nonoperative treatment of hydrocele is often unsatisfactory. Simple aspiration is followed by early recurrence of the fluid and sometimes by infection.

The injection treatment often fails to cure the hydrocele and frequently results in the formation of painful adhesions.

Complete excision of the sac has encountered the objection that many blood vessels which require ligation may be found, and after ligation has been done postoperative extravasation of blood may occur. The bottle operation with inversion of the sac, a procedure introduced to avoid these operative difficulties, is not infrequently unsuccessful and leaves a large mass situated back of the testicle and epididymis.

A new operation has been devised by Young which provides for incision of the sac layer by layer and stripping of the layers back until thin serous membrane is reached; this alone is excised. In this way hemostasis is easily secured, since few vessels remain to be ligated. The operation is thus made more nearly accurate and less destructive and hemorrhagic than other procedures, and it is radically curative.

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73. Young, H. H.: Radical Cure of Hydrocele by Excision of Serous Layer of Sac, Surg., Gynec. & Obst. **70**:807-812 (April) 1940.

GLANDULAR THERAPY

Heckel [74] reported that testosterone propionate injected daily into muscle produced little improvement in the symptoms and clinical course of 22 patients who had benign prostatic hypertrophy. It did not produce any noteworthy reduction in the amount of residual urine. Histologic examination of tissue from the prostate glands of patients who previously had been treated with testosterone propionate disclosed no variation from the appearance of sections from untreated patients. Testosterone propionate produces a temporary depletion of spermatozoa in patients who have spermatozoa in normal numbers. In 10 of 12 patients oligospermia was produced. These data would indicate that this material is of little benefit in the treatment of benign prostatic hypertrophy, and its promiscuous use for a long period for patients who have normal testicular function might be harmful.

Korenchevsky and Ross [75] have noted in previous publications that the weight of the kidney in rats was decreased after castration and increased after injection of androgens. They noted also that there was an apparent decrease in the size of the kidneys after ovariectomy. Simultaneous injection of both androgens and estrogens produced hypertrophy of the kidneys. Their latest investigation was made to correlate and confirm the previous observations.

The total number of normal rats investigated was 148, of which 70 males and 12 females were kept as controls and 31 males and 35 females were given injections. The total number of gonadectomized rats was 418, of which 59 males and 21 females were controls; 142 males and 39 females were given injections of androgens; 20 males and 34 females were given injections of estrone, estradiol or esters of the latter; and 48 males and 55 females were given simultaneous injections of both androgenic and estrogenic substances.

The experiments were carried out on 178 rats for twenty-one days and on the remaining 388 rats for two to three and three-quarters months.

In agreement with the absence of any definite change in weight of the kidneys, no significant change in the size of the tubules, either by weight or histologically, was found in ovariectomized rats. In castrated rats the measurements showed a definite decrease in the size of the convoluted tubules. Thus, the definite decrease in the size of the kidneys

74. Heckel, N. J.: The Influence of Testosterone-Propionate upon Benign Prostatic Hypertrophy and Spermatogenesis: A Clinical and Pathologic Study in the Human, Tr. Am. A. Genito-Urin. Surgeons **32**:237-261, 1939; J. Urol. **43**:286-308 (Feb.) 1940.

75. Korenchevsky, V., and Ross, M. A.: Kidneys and Sex Hormones, Brit. M. J. **1**:645-648 (April 20) 1940.

after castration can be explained by slight atrophy of the tubular secretory apparatus in these organs.

In both normal and gonadectomized female rats and castrated male rats, the androgenic substances, androsterone and esters of testosterone, produced true hypertrophy of the kidneys and could therefore be defined as nephrotrophic substances.

The action of testosterone esters on the kidneys appears to be definitely beneficial. On the other hand, when estrogens were injected into the animals for prolonged periods, there was no increase in the weight of the kidneys or in the size of the tubules, but there was cystic degeneration of the tubules in the boundary layer of the cortex and medulla, with atrophy of the tubular epithelium and marked peritubular edema.

When the androgens and estrogens were injected simultaneously into the rats, the hypertrophizing effect of the androgens remained the same. The pathologic effects of the estrogens (dilatation of the tubules, formation of small cysts and development of peritubular edema and hyperemia) were prevented or decreased by the neutralizing effect of the androgens in some rats only. Some animals were as well developed as animals that had received injections of estrogens alone.

Since androsterone has only a weak action on the female sex organs and occurs normally in the female organism, this substance might also be cautiously tested in suitable renal diseases of women.

In women suffering from these diseases, however, the administration of estrogens, especially in large doses or for prolonged periods, probably would increase the pathologic changes in the kidneys.

Merk [76] tried treatment with testosterone propionate in a series of cases of prostatic enlargement. No success was obtained in 10 cases in which large prostatic adenomas and large amounts of residual urine were present. In 32 instances of early enlargement in which less than 100 cc. of residual urine was present, symptoms of prostatism disappeared after twelve injections of 10 mg. of the substance. Most of the patients said that they felt much better after the treatment.

In 20 cases in which it was necessary to do some kind of operation, the general condition of the patients was considerably improved by injections. Merk discontinued the glandular treatment one week before operation and did not continue it after operation, since he was of the opinion that severe hemorrhage may develop as a result of hyperemia caused by the glandular substances.

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76. Merk, K.: Ueber die Verwendung synthetischen Testishormons in der konservativen und chirurgischen Therapie der Prostata-Hypertrophie, Ztschr. f. Urol. **33**:573-577, 1939.

VITAMIN THERAPY IN UROLOGY

Wildbolz [77] carried out systematic investigations of the ascorbic acid metabolism of patients who had various urologic and surgical lesions. He found that such patients rarely suffered from hypovitaminotic conditions. There was no regular parallelism between recovery or therapy and vitamin C content, and he was unable to reduce the number of postoperative complications by therapy with vitamin C.

HEMATURIA

McKenna and Birch [78] stated that there is a group of cases in which hematuria is present, either alone or accompanied with other hemorrhagic phenomena, and in which there is no demonstrable pathologic condition of the urogenital tract. The causative factor is a pathologic condition of the elements of the blood or of the capillaries. The most important conditions are the purpuras, essential or symptomatic, hemophilia and avitaminosis C. Not infrequently hemorrhage from the kidney is the most prominent symptom, and occasionally it may be the only symptom, so that the patient is referred to the urologist. It is essential that such conditions as these be recognized and evaluated, because urologic manipulation or surgical treatment will do the patient no good whatever and may be definitely harmful. Every patient who has hematuria of unknown causation should have the benefit of complete studies of the blood and also of determinations of the ascorbic acid content of the blood.

CARCINOGENIC AGENTS

Caldwell [79] stated that various hydrocarbons, derived from coal tar or synthetically prepared, will produce cancers in experimental animals of different species. The tumors produced are either carcinomas or sarcomas, depending chiefly on the application of the active agent to the epithelium of the surface of the skin or the introduction of the agent into the deeper tissues. The latent period preceding the appearance of the tumor is relatively long, and its length seems to have some relation to the life span of the particular species of animal used.

The estrogens, administered in huge doses, are undoubtedly carcinogenic, and in susceptible strains of animals even physiologic concentrations seem to determine largely what the incidence of tumors will

77. Wildbolz, E.: Systematische Untersuchungen über die Rolle des Vitamins C in der Chirurgie und Urologie, Ztschr. f. Vitaminforsch. **9**:223-238, 1939.

78. McKenna, C. M., and Birch, C. L.: Hematogenous Hematuria, J. Urol. **42**:171-182 (Aug.) 1939.

79. Caldwell, G. T.: Chemical Carcinogenic Agents, J. Urol. **42**:651-673 (Nov.) 1939.

be in those organs which are subject to repeated stimulation by means of these substances.

Many tumors produced by chemical agents in one animal have been transplanted into other animals of the same species, and some have been transferred in this way through many generations. Apparently, stimulation by the original carcinogenic agent is no longer necessary for the subsequent growth of the tumor. The cells which constitute the tumor seem to have acquired new characteristics, and these characteristics, whatever they may ultimately prove to be, are transmitted without fail to all tumors which stem from the original tumor by the experimental process of transference.

UROLITHIASIS

Flocks [80] stated that the level of urinary calcium is a very important link between calcium metabolism and the development of calcium urolithiasis.

The excretion of calcium in the urine of the normal person and in that of the person who is undergoing certain intrinsic changes in his body mechanisms is discussed. More specifically, the effects on the urinary calcium of bodily immobilization, intrinsic osseous disease, certain endocrine changes, certain intrinsic renal changes and certain intrinsic variations the mechanism of which is not as yet understood are described. The possibility of increasing and decreasing the excretion of calcium in the urine under these several conditions by means of changes in the patient's calcium and phosphorus intake, acidity of the ash of the diet and vitamin D intake is discussed.

The management, from the point of view of calcium metabolism, of the patient who has calcium urolithiasis is discussed under three headings: (1) the prophylaxis of urolithiasis for patients who have conditions in which the urine has a high content of calcium; (2) the management of patients who have calcium urolithiasis and in whose urine the content of calcium is high, and (3) the management of patients who have calcium urolithiasis and whose urine has a normal or a low content of calcium.

Eisele [81] analyzed the records of all patients from the University of Chicago Clinics between 1927 and 1939 who had ureteral or renal calculi. He did this with the object of determining the relation between the treatment of peptic ulcers and the formation of urinary stones.

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80. Flocks, R. H.: Calcium Urolithiasis: The Rôle of Calcium Metabolism in the Pathogenesis and Treatment of Calcium Urolithiasis, J. Urol. **43**:214-233 (Jan.) 1940.

81. Eisele, C. W.: Role of Alkali Therapy for Peptic Ulcer in Formation of Urinary Calculi, J. A. M. A. **114**:2363-2366 (June 15) 1940.

Conditions favorable to formation of stone are produced by the usual medical treatment of ulcer, namely, increase in urinary solids, high specific gravity, excretion of large amounts of crystalloids and a shift of the p_H of the urine to the alkaline side. Theoretically, hyperexcretory calculosis should be common among patients who are under treatment for ulcers.

Eisele found that, among 505 patients who had renal or ureteral calculi, 43, or 8.5 per cent, had peptic ulcers of which the symptoms antedated the symptoms referable to stone, and all of the patients had received the Sippy type of treatment. In addition, 13 patients, or 2.6 per cent, had chronic gastrointestinal distress and habitually took large amounts of alkalis for relief. Thus, there were 56 patients, or 11.1 per cent, among those who had lithiasis, in whom the ingestion of alkalis may have played a role in the formation of urinary stones.

The hyperexcretory calculosis which developed in these patients demonstrates the potential danger of alkali therapy for patients who have peptic ulcers.

CHANCROID

Schwartz and Freeman [82] discussed sulfanilamide in the treatment of chancroid and reported a series of 37 cases. For comparison there was also presented, as a control group, a series of 60 similar cases in which the patients were treated by other methods.

Various doses administered daily were used and evaluated. The average dose for the total group was 46 grains (3 Gm.) of sulfanilamide a day. The total dose varied between 280 and 950 grains (18 and 62 Gm.) and averaged 642 grains (42 Gm.) per patient. After the initial dose of from 3 to 4 Gm., the maintenance dose was determined by the clinical response and by the weight and age of the patient. A high maintenance dose is of the utmost importance. The least desirable combination is a low initial dose and a low maintenance dose. The next least desirable is a high initial dose and a low maintenance dose. The combination of a low intial dose and a high maintenance dose is more desirable, whereas the combination of a high initial dose and a high maintenance dose is the most desirable.

Including all the various types of lesions, the average period required for healing in the control group was slightly more than thirty-two days. In comparison, for the patients treated with sulfanilamide this time varied from seven to twenty-three days and averaged fifteen and seven-tenths days. Chancroidal ulcers situated elsewhere than on the glans penis responded best to treatment. Chancroidal bubo, unruptured, was next most responsive. There was little difference in the response

82. Schwartz, W. F., and Freeman, H. E.: Sulfanilamide in the Treatment of Chancroid, J. A. M. A. **114**:946-947 (March 16) 1940.

to sulfanilamide of ruptured, chancroidal bubo, and the response of ulceration of the glans penis, but the latter lesion was slightly less responsive.

ENURESIS

Sitkéry [83] reported a series of 196 cases of enuresis in which he had done manometric examinations of the bladder. He concluded that the underlying pathologic process is an increased irritability in the afferent nerve fibers of the bladder. This irritability causes pollakiuria, which Sitkéry stated is identical to, and always associated with, enuresis. He therefore preferred to call this condition "pollakiuria enuretica."

URINARY ANTISEPTICS

Weyeneth [84] reviewed the literature on mandelic acid and presented the results of treatment of urinary infections obtained in the Geneva Medical Clinic with the new compound amanol. Amanol, which contains mandelic acid, combines in a 1 Gm. tablet the following substances: methenamine phenylglycolicum, 0.2 Gm.; calcium phenylglycolate, 0.7 Gm.; sulfanilamide (paraaminobenzenesulfonamide), 0.1 Gm. In the treatment of advanced types of urinary infection, including that caused by Bacillus coli, and also in the treatment of mixed infections the results have been uniformly good. In cases of complicated urinary infections aggravated by stones and tumors, the results naturally were not so satisfactory. It is necessary, as in the treatment with simple mandelic acid, that the intake of fluids be restricted. Weyeneth stated that the main advantages of amanol over other mandelic compounds is that it is well tolerated by the stomach.

Buchtel and Cook [85] reported the results of neoarsphenamine therapy for infection of the urinary tracts of 258 patients, 149 males and 109 females ranging in age from 10 to 77 years. Diagnostically, especially in the presence of coccic infections, Gram's stain of the centrifuged urinary sediment is more valuable even than special culture mediums. The presence of either bacteria or pus in the urine is good evidence that disease exists in the upper part of the urinary tract and not in the prostatic region.

The criteria for cure of bacillary infection in men were absence of bacteria and pus in the urine and sterile prostatic cultures. For women these criteria were absence of bacteria and pus in the urine and absolute

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83. Sitkéry, J.: Untersuchungen über die Pathologie der sogenannten Enuresis nocturna, Ztschr. f. Urol. **33**:409-421, 1939.

84. Weyeneth, R.: Die Mandelsäure in der Bekämpfung der Harnweginfektionen unter kritischer Berücksichtigung eines Zweckmässig kombinierten Therapeutikums, Schweiz. med. Wchnschr. **69**:1297-1302 (Dec. 23) 1939.

85. Buchtel, H. A., and Cook, E. N.: Neoarsphenamine in the Treatment of Urinary Infections, J. Urol. **43**:417-426 (Feb.) 1940.

relief of symptoms. Final certainty of cure was assumed if no recurrence was noted during the first three months after cessation of treatment.

Bacillary infection responded very poorly to neoarsphenamine therapy, as did nonspecific prostatitis. Infection caused by Streptococcus faecalis responded to acidification therapy alone or in combination with neoarsphenamine. Instances of so-called amicrobic pyuria, in which bacteria could not be demonstrated in the urine even after special efforts, did not respond. However, if bacteria were demonstrated, results were satisfactory. Response to treatment was better in cases in which the upper part of the urinary tract was involved than in those in which the bladder was involved. These results were especially favorable in cases of uncomplicated infection.

Improvement usually appeared after the first injection of neoarsphenamine. Increasing doses should be used in subsequent injections in cases in which there has been no response. Only two doses should be administered in cases in which no improvement is demonstrated. Results were better when they were accompanied by urinary acidification. Four doses are all that are usually indicated.

Of the 189 patients who had coccal infections and who were treated with neoarsphenamine, 17 per cent had reactions, which is a higher proportion of reactions (and the reactions were of a more severe type) than is the case when neoarsphenamine is used specifically.

UROGRAPHY

Braasch and Doss,[86] in discussing the clinical value of the delayed urogram, said that the difficulty in determination of the cause of stasis visualized in the delayed urogram often diminishes its clinical value. It is possible that more precise methods of determining the ureteropelvic physiologic picture than have been employed in the past may aid in this respect. However, the delayed urogram is often of definite value in determining ureteropelvic obstruction, particularly in "borderline" cases. Unless the existence of stasis can be visualized in these cases, surgical intervention usually is not indicated. The delayed urogram also may be of value in the identification of doubtful roentgen shadows in the ureter or kidneys. In spite of the fact that the observations are sometimes puzzling, the method deserves more frequent employment.

RETROPERITONEAL TUMORS

Kretschmer[87] reported a case of retroperitoneal lipofibrosarcoma in which the patient was a child.

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86. Braasch, W. F., and Doss, A. K.: The Clinical Value of the Delayed Urogram, Tr. Am. A. Genito-Urin. Surgeons **32**:119-125, 1939.

87. Kretschmer, H. L.: Retroperitoneal Lipofibrosarcoma in a Child, Tr. Am. A. Genito-Urin. Surgeons **32**:57-71, 1939.

It is generally noted that the age of patients in whom retroperitoneal lipoma occurs with greatest frequency is from 40 to 60 years. In the series of 42 cases studied by Pemberton and McCaughan, the youngest patient was 28 years old; the oldest was 68 years old, and the average age was 49.3 years.

This tumor may reach enormous proportions. One of the largest tumors was that described by Hirsch and Wells, which weighed 69 pounds (31.3 Kg.). From the standpoint of clinical pathology, retroperitoneal lipomas present two very interesting aspects: (1) recurrence is relatively frequent with growths that are histologically benign and (2) in certain cases a recurrent tumor which originally had been histologically benign shows malignant changes.

Concerning the point of origin, it may be said that this frequently is hard to determine, except for the fact that it is known that the tumor arises in the retroperitoneal space. When the tumor comes to clinical observation and operation, it has, in the average case, reached huge dimensions and fills much of the retroperitoneal space. There is a general tendency for urologists to regard all such tumors as simply retroperitoneal rather than to try to distinguish those arising from the root of the mesentery or those which are perirenal in origin. Mayo and Dixon found that 80 per cent of simple retroperitoneal lipomas arose in the abdomen and that 20 per cent arose in the pelvic region.

As a result of the growth of the retroperitoneal lipoma, secondary changes may occur in the urinary tract which may lead to complete destruction of the kidney. Displacement and compression of the ureter may result in hydronephrosis. A large retroperitoneal lipoma may envelop the kidney so that pressure atrophy results, or the kidney may show more or less dilatation caused by obstruction at the ureteropelvic junction or below that point. Not infrequently a retroperitoneal fatty tumor surrounds the kidney and its pelvic structures so completely that removal of the mass necessitates nephrectomy. This operation was done in 50 per cent of the reported cases.

In the majority of reported cases the tumor had caused no symptoms until it reached such a size that abdominal swelling was noted or until it produced pressure symptoms on various organs (usually the digestive or the genitourinary tract).

Radical extirpation is the only possible treatment of retroperitoneal lipomatous tumors. Since in most cases symptoms are absent until the growth has attained a huge size, the operation is necessarily very difficult, considering the adhesions frequently encountered and the close proximity of the growth to important structures and to large blood vessels. In the case reported by Kretschmer the operation was easily carried out. The entire tumor was shelled out as easily as any lipoma could be shelled out except that adhesions were present at the upper pole, where the tumor was firmly attached to the muscles of the back.

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